VOLUME 52 NUMBER 5

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ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY

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NOTE

Owing to a strike of printers in the press of the American Medical Association, publication of all of the special periodicals of the Association has been considerably delayed. In order to bring these periodicals up to the normal schedule, the November and December numbers are combined into a single issue. Regular publication will be resumed with the issues for January 1946.

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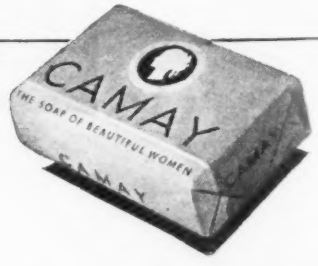

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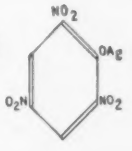

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Sweet, L. K., and Putnam, L. E.: M.Ann. District of Columbia 14:148 (Apr.) 1945.

25,000 units of penicillin administered intramuscularly every 3 hours to an average total dosage of 400,000 units resulted in bacteriological cure in 13 women with verified acute gonococcal pelvic inflammatory disease. No therapy other than penicillin was used.

Gray, L. A.: South.M.J. 38:405 (June) 1945.

Of 108 hospitalized adult females with gonococcus-positive cultures and/or smears, 101 had failed to respond to sulfonamides. All but one patient became bacteriologically negative within 24 hours of termination of penicillin treatment. The authors recommend three 3-hourly intramuscular penicillin injections of 50,000 units, followed by two 25,000-unit injections.

Cohn, A.; Taylor, H. C., Jr., and Grunstein, I.: Am.J.Obst.&Gynec. 49:657 (May) 1945.

15 of 16 cases of gonorrheal vaginitis in children aged 1 month to 11 years were cured with a single intramuscular injection of 100,000 units of penicillin. The one failure responded to an additional course of 80,000 units — 10,000 units every 3 hours.

Sako, W.; Tilbury, R., and Colley, J.: J.A.M.A. 128:508 (June 16) 1945.

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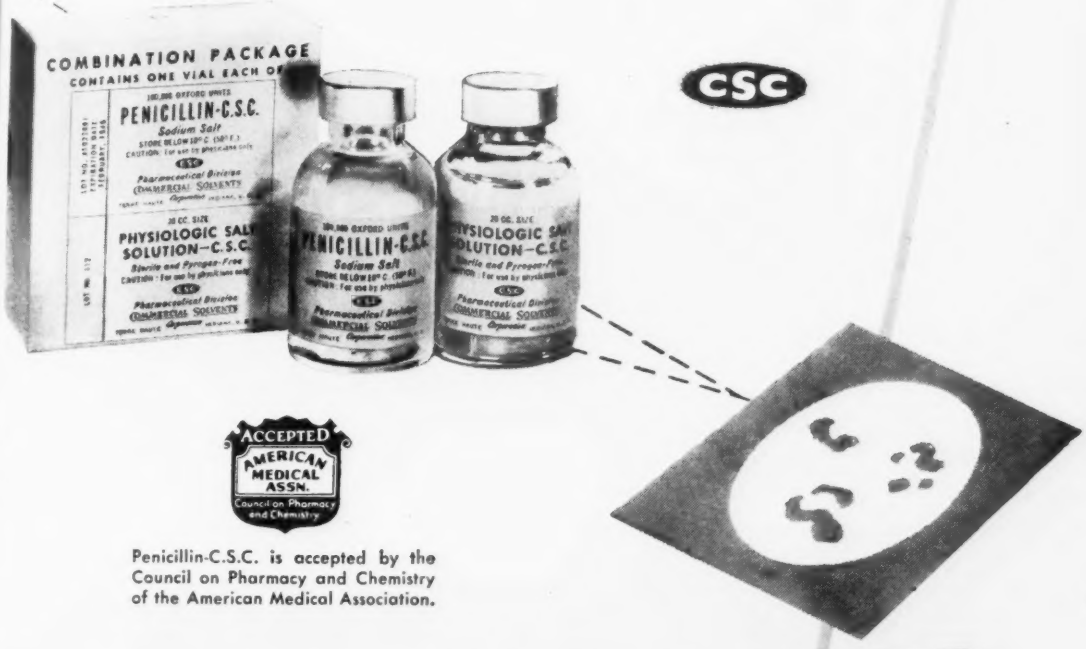

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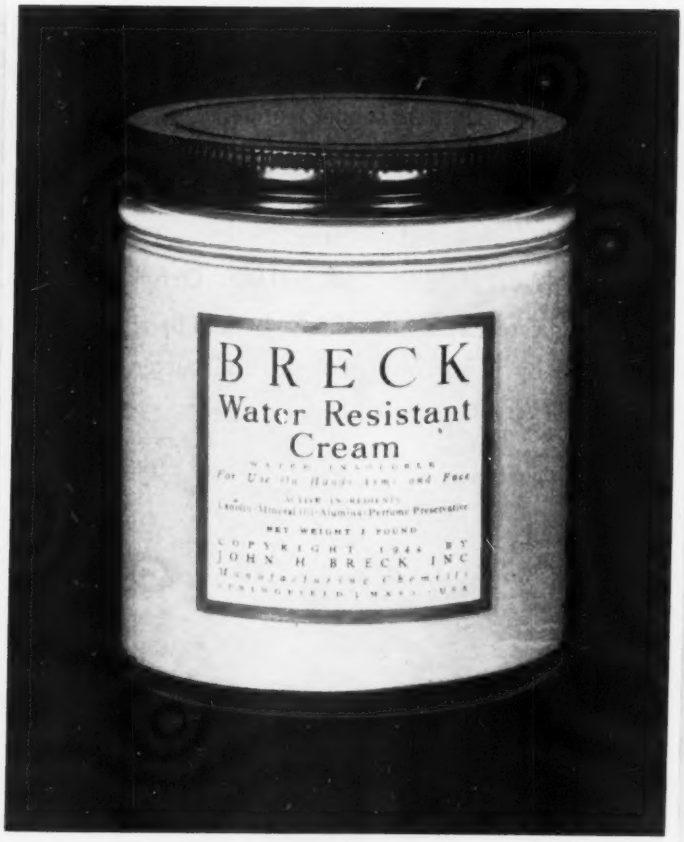

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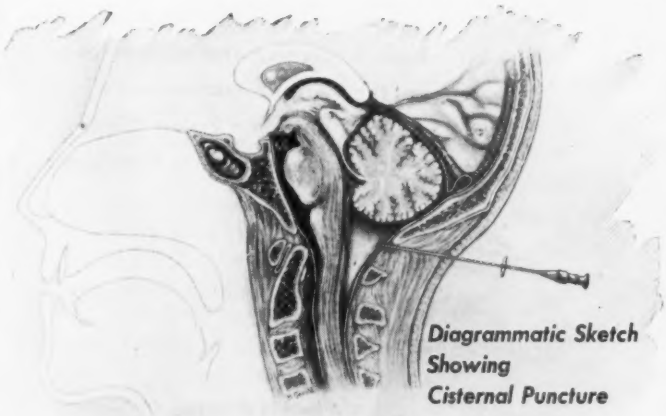

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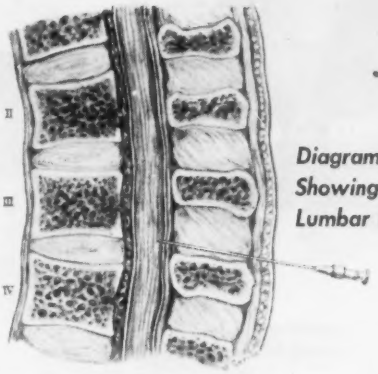

Diagrammatic Sketch Showing Lumbar Puncture

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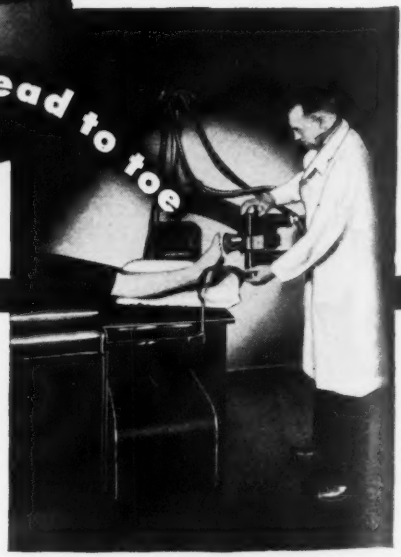

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Archives of Dermatology and Syphilology

VOLUME 52 NOVEMBER-DECEMBER 1945 NUMBER 5

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CARBOHYDRATE METABOLISM AND THE SKIN

ERICH URBACH, M.D., AND JOHN W. LENTZ, M.D.
PHILADELPHIA

For many years one of us (E. U.)[1] has pointed to the fact that in the study of the physiology and pathology of the skin a chemical analysis of the skin excised from the living organism gives a far better insight into the metabolic processes of that organ than does a study of the blood alone. With regard specifically to the carbohydrate metabolism of the skin, the blood sugar tolerance test, which is generally so dependable, has been found unreliable in a number of instances.[2] Urbach[3] has introduced the electric punch biopsy method, with which skin can be removed almost painlessly, without anesthetics of any kind, even when the procedure is performed repeatedly for a series of studies. At the same time, microchemical methods have been perfected which make it possible to carry out an accurate determination of sugar in minute tissue particles. This method has been used to determine the free[4] and bound[5] sugar in the normal skin of man and animals and also to study the carbohydrate metabolism of the skin under pathologic conditions and in a variety of cutaneous diseases.

Since some of these investigations were originally carried out in Vienna, on persons whose diet was much higher in carbohydrate and fat than the usual American diet is, we decided that we might profitably repeat these studies here with a larger experimental material. For this purpose 60 biopsy specimens were obtained in duplicate from 36 patients with various diseases of the skin and 10 persons, used as controls, who were free from cutaneous manifestations and from diabetes. In addition, the results of a previous similar study[4] carried out on 90 patients are incorporated in this report.

The 36 patients who were more recently studied consisted of 11 with eczema of various causation, 7 with psoriasis, 6 each with staphylococcic infection and mycotic infection, 2 each with pruritus and xanthoma tuberosum and 1 each with rosacea and epithelioma of the face. Three of the 36 patients had diabetes mellitus; added to 9 previously reported diabetic patients makes this a total of 12 (table 8).

In 7 cases determinations of the sugar in the blood and in the skin were repeated three times within five to six weeks. The first time the patients were on their usual diets; the second time as nearly as possible on a carbohydrate-free diet, and lastly on a regimen very low in fat. In the last instance, 3 patients were also restricted in their consumption of carbohydrates.

Lastly, the relative proportions of skin sugar to blood sugar were studied in six different species of animals.

BIOPSY PROCEDURE

Two specimens of skin are excised by means of a rapidly rotating, motor-driven punch, 5 mm. in diameter. The punches are inserted into the shaft of a small motor[6] of the kind ordinarily used in hand drills. With this device, uniform pieces of skin can be removed within a few seconds. The pieces are snipped off at the base with the scissors. The wound is then briefly swabbed with a 2 per cent aqueous solution of gentian violet medicinal followed by thymol iodide powder for disinfection purposes. When the operation is performed rapidly, the excised piece of skin is free of blood. Great care must be taken to remove the subcutaneous fat

Expenses for this work were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia.

From the Department of Dermatology and Syphilology, University of Pennsylvania School of Medicine; Dr. John H. Stokes, Director.

1. Urbach, E.: Die biologisch-chemische Forschungsrichtung in der Dermatologie, Wien. klin. Wchnschr. **41**:581, 1928.

2. Urbach, E.; Depisch, F., and Sicher, G.: Zum Problem des isolierten hohen Hautzuckers bzw. Hautdiabetes, Klin. Wchnschr. **16**:452, 1937.

3. Urbach, E., and Fantl, E.: Methoden zur quantitativ-chemischen Analyse der Haut: I. Allgemeine Prinzipien, Biochem. Ztschr. **196**:471, 1928.

4. Urbach, E., and Sicher, G.: Der Zuckergehalt der Haut unter physiologischen und pathologischen Bedingungen, Arch. f. Dermat. u. Syph. **157**:160, 1929.

5. Urbach, E., and Rejtoe, K.: Ueber den freien und "gebundenen" Zucker in der Haut unter physiologischen, experimentell veraenderten und pathologischen Bedingungen bei Mensch und Tier, Arch. f. Dermat. u. Syph. **166**:478, 1932.

6. Hand—EE # 13 aAB, manufactured by the Chicago Wheel and Mfg. Co., 1101 W. Monroe Street, Chicago. Punches manufactured by Jerome Ward, 1315 McKinley Street, Philadelphia.

from the biopsy specimens; and with some experience this is easy enough to do when dealing with human skin, for the yellowish fat can readily be distinguished from the white tissue of the cutis. Dog's skin presents greater difficulties in this respect; for the fat which is closely interwoven with the lower layers of the cutis has the same whitish color as the cutis. In order to obtain corresponding values in both specimens, it is necessary to remove the subcutaneous fat up to the dark upper layer of the cutis, studded with hair follicles.

For the purpose of uniformity the specimens of skin are usually taken from the upper third of the exterior aspect of the thigh because the various areas of skin present appreciable differences so far as their water content is concerned (Nadel [7]). This, of course, has an influence on the sugar content. The specimens of skin usually weigh from 30 to 40 mg., but they may weigh between 20 and 50 mg., depending on their texture, on the skin's state of nourishment and on the age and race of the patient.

In our work with dogs we always put the animals to sleep in order to obviate an increase in blood sugar due to emotional disturbance such as fear or struggle against bonds. The narcotic used was chloralose, of which 0.1 Gm. per kilogram of body weight in a 10 per cent solution in 10 per cent alcohol was administered intravenously. Anesthesia sets in immediately and lasts about four hours. The animals must be kept well covered for the duration of the experiment, otherwise they may suffer fatal chills. Preliminary experiments have convincingly demonstrated that the sugar level in the blood and the skin was not appreciably influenced by chloralose narcosis.

In our earlier experiments we employed the microchemical method suggested by Urbach and Fantl,[8] which was based on the principle of the Hagedorn-Jensen method. Pillsbury and Kulchar [9] checked this procedure in experiments on amytalized rabbits and guinea pigs and obtained similar reliable figures for skin sugar. It was subsequently discovered, however, that the values originally given for free sugar were too low, because a part of the sugar in the tissues had escaped chemical detection as a result of the presence of considerable quantities of amino acid nitrogen in the skin.[5] We eliminated this error by employing Rappaport's [10] method, which achieves precipitation in an alkaline medium. The values determined by means of the improved method were found to be about 20 per cent hig in human beings than the previously repor figures.

An advantage offered by this method is th it enables the investigator to determine the pr cise sugar content of biopsy specimens weighi no more than 20 to 30 mg. This, in turn, pe mits the use of smaller pieces of skin than fo merly, which obviates the necessity of sutur the wounds.

Since it is somewhat difficult to obtain a de scription of Rappaport's procedure, we sha describe it here in detail.

CHEMICAL PROCEDURE

Principle: Heated potassium ferricyanide is reduced b sugar, and the excess of ferricyanide is iodometri cally determined.

Reagents for Dealbumination

(1) 0.45 per cent zinc sulfate solution made from 45 per cent stock solution.

(2) Fiftieth-normal sodium hydroxide.

Reagents for Sugar Determination

(3) A potassium ferricyanide and phosphate buffe solution made (*a*) by dissolving 0.9 Gm. of ferri cyanide in water and diluting to 1 liter in measuring flask; and (*b*) by dissolving 210 Gm of potassium dihydrogen phosphate and 63.75 Gm of potassium orthophosphate in water and dilut ing to 1 liter. The ferricyanide solution and th phosphate buffer should be mixed in equal part before using.

(4) Zinc sulfate-potassium iodide: To 20 per cent zinc sulfate solution (prepared from pure zinc sulfate dissolved in distilled water) add just before using enough solid potassium iodide to form a 2.5 per cent potassium iodide solution. This reagent should be prepared freshly every day.

(5) 20 per cent phosphoric acid: Dilute 20 cc. of syrupy phosphoric acid with water to make 100 cc. of solution.

(6) Thousandth normal sodium thiosulfate: To 10 cc. of tenth-normal sodium thiosulfate add 12 cc. of normal sodium hydroxide in a 1,000 cc. flask and dilute to the mark.

(7) 0.25 per cent starch solution.

Procedure for Venous Blood: For each weighing glass (65 by 16 mm.) use three control glasses. Fill each glass with 1 cc. of sodium hydroxide (reagent 2). Take up 0.02 cc. of blood with an exactly calibrated capillary pipet. Carefully clean the pipet of any blood adhering to the outside and blow the contents into the sodium hydroxide solution. Clean the pipet by taking up and blowing out the sodium hydroxide three times.

Then add 1 cc. of zinc sulfate (reagent 1) and put the glasses into boiling water for three minutes. Cool to room temperature and filter through small funnels (diameter of upper edge 25 to 30 mm., stem thinned out near the top end), which contain a small roll of absorbent cotton washed with hot water, into Hagedorn-Jensen test tubes.

Wash the glasses three times with 1 cc. of hot water and pour the wash water onto the filter. Let the liquid drain thoroughly, then press the cotton with a fine glass rod. Pipet into the test tubes 2 cc. of the ferricyanide-phosphate mixture (reagent 3).

7. Nadel, A.: Chemische Studien an der menschlichen Haut, Arch. f. Dermat. u. Syph. **166**:507, 1932.

8. Urbach, E., and Fantl, E.: Methoden zur quantitativ-chemischen Analyse der Haut, Biochem. Ztschr. **196**:474, 1928.

9. Pillsbury, D. M., and Kulchar, G. V.: The Use of the Hagedorn-Jensen Method in the Determination of Skin Glucose, J. Biol. Chem. **106**:351, 1934.

10. Rappaport, F.: Mikrochemie des Blutes, Vienna, Emil Haim & Co., 1936.

Put the tubes into a boiling water bath for twenty minutes for reduction. After cooling, add 1 cc. of zinc sulfate-potassium iodide solution (reagent 4) and 1 cc. of phosphoric acid solution (reagent 5). Titrate with thousandth normal sodium thiosulfate (reagent 6) from a microburet after adding a few drops of starch solution (reagent 7) until colorless. The change in color is pronounced in spite of the dilute sodium thiosulfate solution.

Calculation:

(Sodium thiosulfate used for control minus sodium thiosulfate used for blood) × 174 equals sugar content in milligrams per hundred grams.

Changes to be Made for Use on Cutaneous Tissue: The weight of a weighing glass with 1 cc. of zinc sulfate solution is determined and a small piece of skin added and the glass weighed again. One cubic centimeter of fiftieth-normal sodium hydroxide is used to wash off the scissors and the forceps used for cutting the skin. Zinc sulfate should be added before the sodium hydroxide when one works with tissue, because the skin swells in the sodium hydroxide and makes it impossible to dissolve out all the sugar.

In order to avoid taking numerous biopsy specimens in the course of lengthy investigations, a number of authors chose to examine dextrose content of blisters induced by cantharides. However, on the basis of painstaking studies [11] we have demonstrated that the fluid from blisters produced by cantharides can definitely not be regarded as chemically representative of cutaneous tissue and cannot, therefore, serve as a substitute for biopsy specimens for chemical investigations.

SUGAR CONTENT OF THE SKIN UNDER PHYSIOLOGIC CONDITIONS IN MAN AND ANIMALS

Free Sugar in the Skin.—Studies on the fasting subjects living under similar dietary conditions reveal that the skin of man and animals presents a relatively constant sugar level. Thus determinations of the fasting skin sugar repeated after eight to ten weeks on several persons on the same diet have shown differences of only 2 to 3 per cent. However, the skin sugar level varies from species to species. Table 1 shows that man has the lowest absolute skin sugar value, an average of 58 mg. per hundred grams. The mean blood sugar level is 94 mg. per hundred cubic centimeters. The proportion of skin sugar to blood sugar is about 61.4 per cent. The sugar content of the skin and its relation to the blood sugar are in no way dependent on the age of the person. On the other hand, as we shall presently demonstrate, dietary habits exert a decided influence in this respect. In this connection it is interesting to note that in Vienna the average values were as follows: blood sugar 103 per hundred cubic centimeters, skin sugar 61 per hundred grams. These figures are definitely higher than those arrived at for our Philadelphia material. This, we feel, may unquestionably be explained by the fact that the usual diet in Austria was appreciably higher in carbohydrates. In animals, with the exception of the mouse, the sugar content of the skin is higher than that of the blood. The highest values for skin sugar are found in guinea pigs and cats.

Bound Sugar in the Skin.—Determination of the rate of the so-called free sugar does not mean that the entire carbohydrate content of the skin has been accounted for. As early as 1855, Fignier observed that the reducing capacity of the blood showed a decided increase after the blood has been boiled with an acid. These reducing substances have generally been termed bound sugar. Bierry coined the term: *sucre protéidique* (protein sugar). Whereas free sugar is composed mainly of glucose, bound sugar, on the other hand, is composed chiefly of mannose and glucosamine. In a previously published paper,[5] we specifically have pointed out that, in addition to the free sugar, the bound sugar contains certain reducing substances which are released by hydrolysis. Therefore, in full agreement with Grevenstuck [12] we should like to stress here that when we employ the term bound sugar we are well aware of the fact that this term is not strictly accurate. To be absolutely correct and specific, we should have to say, at some length, that we are dealing here with a number of substances whose capacity for reducing is increased by hydrolysis with acids.

Urbach and associates [5] have determined the quantity of bound sugar in the skin of man and animals. In the former, it is about fifteen times greater than the value for free sugar in the skin, and one and one-half times that of the

TABLE 1.—*Level of Free Sugar of Blood and Skin in Man and in Animals*

Subject	Mg. Sugar per 100 Cc. Blood	Mg. Sugar per 100 Gm. Skin	Blood/Skin Sugar-Ratio, per Cent
Man	94	58	61
Mouse	114	77	67
Dog	84	87	103
Rat	85	106	125
Rabbit	105	134	128
Guinea pig	110	145	132
Cat	97	148	151

11. Urbach, E.: Ueber den prinzipiellen Unterschied in der chemischen Zusammensetzung von Hautblaseninhalt und intravital entnommenem Hautgewebe, Klin. Wchnschr. **8**:2094, 1929.

12. Grevenstuck, A.: Ueber freien und "gebundenen" Zucker in Blut und Organen, Ergebn. d. Physiol. **28**:1, 1929.

bound sugar in the blood. In animals, the skin also contains far more bound sugar than free sugar, although the preponderance is not as great here as it is in man. This proportional difference is due, in part, to the fact that the free sugar concentration is higher in the skin of animals than in the human skin (table 2). When rabbits are kept on different kinds of diets (green fodder, high carbohydrate diet, mixed

TABLE 2.—*Bound Sugar in the Blood and Skin of Man and Various Animals*

Subject	Total Sugar after Acid Hydrolysis (Bound Sugar)		Ratio of Skin Sugar to Blood Sugar, per Cent
	Mg. per 100 Cc. in Blood	Mg. per 100 Gm. in Skin	
Man	543	884	163
Dog	608	1,082	178
Rabbit	495	885	178
Guinea pig	428	776	181

diet) we find that the animals that have been fed large quantities of carbohydrate show considerable greater amounts of bound sugar in the skin than do those that have been kept on a green fodder diet.

In diabetic human beings and in dogs with experimentally induced diabetes the bound sugar level of the skin is considerably above the normal (table 3). In terms of total bound sugar the skin is surpassed only by muscle tissue due to the great quantitative preponderance of the latter in the body.

On the other hand, there is no demonstrable connection between dermatoses and the bound sugar concentration of the blood, not even when large amounts of sugar are ingested.

TABLE 3.—*Free and Bound Sugar Content of Various Tissues of Pancreatectomized Dog* *

	Free Sugar	Bound Sugar
Blood (mg. per 100 cc.)	320	1,068
Skin (mg. per 100 Gm.)	256	2,329
Subcutaneous fat (mg. per 100 Gm.)	78	542
Muscle (mg. per 100 Gm.)	227	2,276
Liver (mg. per 100 Gm.)	821	2,185

* Examined one week after pancreatectomy.

SKIN SUGAR TOLERANCE TEST

We have also studied the reaction of the skin sugar level to the sugar tolerance test. We [13] prefer the oral to the intravenous method because the former, which comes closer to reproducing the conditions of carbohydrate ingestion, constitutes the better functional test of the pancreas.

13. Urbach, E.: Perorale oder intravenoese Zuckerbelastung zur Pruefung der glykaemischen Reaction? Klin. Wchnschr. **11**:1789, 1932.

When glucose (100 Gm.) is given by mouth the maximal level in the blood is reached within half an hour, while the maximal concentration in the skin is not observed before an hour after administration.

In those cases in which the blood sugar returns to its original level within two hours it takes the skin sugar curve three hours to drop to its starting point, and this takes even an

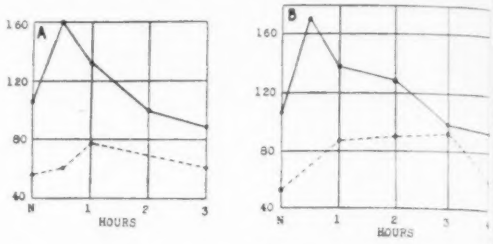

Fig. 1.—Normal sugar tolerance curves of the blood and the skin in man. The unbroken line indicates blood sugar, the broken line skin sugar in all the charts.

hour longer in those not uncommon cases in which it takes the blood itself three hours to register a decline in the hyperglycemia (fig. 1).

SUGAR CONTENT OF THE SKIN UNDER VARIOUS DIETARY CONDITIONS

The opinion is still widely held that the diet has little, if any, influence on the fasting blood sugar level in man and animals. This does not by any means hold true in all cases. In an extensive series of experiments on human subjects we were able to ascertain that the fasting rates

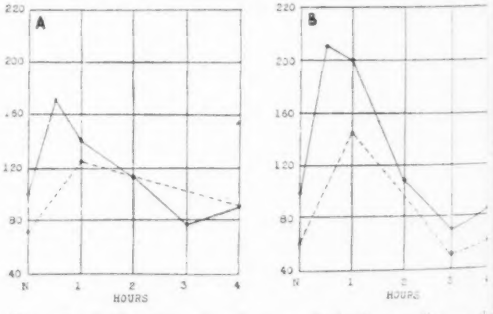

Fig. 2.—Influence of a low carbohydrate diet on the blood sugar curve. *A*, curves when the subject was on the usual diet; *B*, after a diet low in carbohydrates and high in protein.

in both the blood and the skin are directly influenced by the carbohydrate content of the diet.

Even more clearly evident is the influence exerted by the diet on the behavior of the blood sugar curve following administration of massive quantities of sugar. Thus figure 2*B* shows the response of a patient who had been maintained on a carbohydrate-free diet; a blood sugar of

was found thirty minutes after ingestion of 100 Gm. of sugar. On the other hand, when the patient was fed a mixed diet, a level of only 170 was noted, following the glucose meal (fig. 2A). This difference in response can be demonstrated even more strikingly in experiments on animals. For example, when a dog on a diet entirely free from carbohydrates was given sugar, 1.5 Gm. per kilogram of body weight (fig. 3B), the blood sugar rose to 280, as compared with 134 when the animal was kept on a strict carbohydrate diet (fig. 3A). Similar findings have been reported by Himsworth.[14]

man (fig. 2B) and animals (fig. 3B) on a low carbohydrate diet than in subjects that have been on a mixed or a high carbohydrate diet. Moreover, the skin sugar curve like the blood sugar curve rises steeply one hour after administration of sugar and then returns rapidly to normal or even subnormal levels (figs. 2B and 3B). These pathologic curves may serve as a warning against carrying out glucose tolerance tests when the patient is on a low sugar diet.

Toshima[16] kept rabbits on a diet extremely rich in sugar for three months and noted, in agreement with our findings, that the fasting

TABLE 4.—*Influence of Low Carbohydrate Diet on the Fasting Sugar Content of Blood and Skin*

Patient	Age	Sex	Disease	After Normal Diet			After Low Carbohydrate Diet (3 Weeks)		
				Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio
M. W.	45	F	Psoriasis	104.2	63.4	60.8	90.3	55	60.9
E. B.	44	M	Furunculosis	113	69.4	61.4	86.8	53.8	61.9
A. W.	38	M	Dermatophytosis	113.2	68.1	60.1	93.2	57.8	62.0
S. B.	30	M	Xanthoma	111.2	64.4	59.3	97.1	59.8	61.6
W. M.	70	M	Epithelioma	105	63.5	60	86.9	53.7	61.7

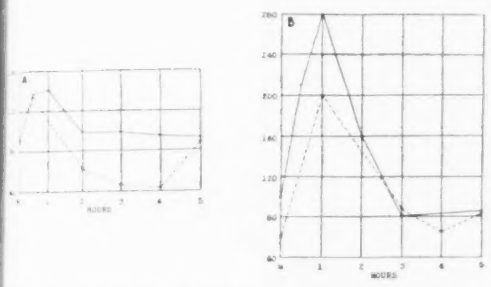

Fig. 3.—Influence of various diets on the sugar tolerance curves of blood and skin in the same dog. *A*, curves after a dog had received a pure carbohydrate diet for a week; *B*, after it had received a pure meat diet for a week.

In our opinion, this sugar curve is not, as Uchida[15] and other authors claim, similar to a diabetic response; we feel that it is to be interpreted as a glycemic reaction of the sympathetic type (see following text). Our views are based on the facts that (1) the peak of the reaction is speedily reached, (2) the level soon returns to normal, and, above all, (3) the curve shows an ensuing hypoglycemia.

The skin responds in a similar manner. The fasting skin sugar level is definitely lower in blood and skin sugar levels were definitely higher than in animals on a normal diet.

Tsukada's[17] experiments are especially interesting. They demonstrate that while the skin sugar level is largely dependent on the acid or alkaline character of the diet, the blood sugar is more or less independent of the acidity of the food. For example, in animals fed on oats or cabbage the skin sugar tolerance shows appreciable fluctuations, while the blood sugar remains virtually constant in almost all cases. The skin sugar tolerance is increased by an acid ash diet (oats) and decreased by alkaline ash food (cabbage). Similarly, hydrochloric acid and sodium bicarbonate, administered by mouth, exert an influence on the skin's capacity to absorb sugar, the former increasing and the latter decreasing this capacity.

Thus, Tsukada's investigations disclose the highly significant fact that not only the carbohydrate content of the diet, but also its acid and base constituents exert a definite influence on both the sugar level and the sugar tolerance of the skin. Further studies carried out by this author would seem to warrant the assumption that other contributing factors, such as the auto-

14. Himsworth, H. P.: Mechanism of Diabetes Mellitus, Lancet **2**:1, 1939.

15. Uchida, K.: Untersuchungen ueber den Einfluss von Traubenzucker und Dioxyaceton auf den Blutzuckerspiegel unterwechselnden Bedingungen, Biochem. Ztschr. **194**:111, 1928.

16. Toshima, E.: Hautzucker bei Zuckerstoff-Ueberfuetterung, Jap. J. Dermat. & Urol. **36**:405, 1934.

17. Tsukada, S.: Experimentelle Untersuchungen ueber die Schwankung des Haut- und Blutzuckergehaltes unter verschiedenen Bedingungen, Tohoku J. Exper. Med. **21**:347, 1933.

nomic nervous system and the ductless glands, may exert an influence on the skin's capacity to absorb and to release sugar, often independently of the blood sugar.

As mentioned before, Urbach and Rejtoe [5] have shown that animals on a high carbohydrate diet possess considerably greater quantities of bound sugar in the skin than do those animals that have been kept on a normal diet.

Especially interesting is the question as to the influence which either a high fat or low fat diet may have on the carbohydrates of the blood and of the tissues. With regard to a diet high in fat, Adlersberg and Porges [18] have pointed out that in diabetic persons this kind of diet seriously disturbs the capacity to assimilate carbohydrates and greatly lowers the sugar tolerance. Stolte,[19] as well as Hirsch-Kauffmann and Knauer [20] have demonstrated that a high fat intake creates a frank hyperglycemia in diabetic and nondiabetic persons alike. According to Himsworth [21] both men and animals kept on a diet high in fat present more prolonged and far more pronounced hyperglycemia following administration of glucose than do subjects on a diet high in carbohydrates.

In experiments on rabbits, Sikinami and Hosokawa [22] claimed that administration of fat, in the form of 2 cc. of cod liver oil, resulted in a greater increase in the sugar content of the skin than in that of the blood. They obtained the same response from a single administration as from repeated doses of cod liver oil. However, investigations carried out by ourselves [22a] gave rather different results as far as the influence of fat intake on skin sugar is concerned. As can be seen from table 5, the administration of 2 cc. of cod liver oil to fasting rabbits previously on a normal diet produced a progressive decrease in the skin sugar amounting to more than 10 per cent after three hours, while at the same time the blood sugar showed a slight tendency to increase.

This trend was even more pronounced when animals were fed 2 cc. cod liver oil daily for one week (table 6). The fasting skin sugar of rabbits so prepared shows a drop of about 10 per cent while the blood sugar is practically unchanged.

The explanation of the difference between our observations and those of Sikinami and Hosokawa is in all probability a faulty method used by the Japanese authors in determining skin sugar. It is sufficient to state that their skin sugar levels are far below the blood sugar levels.

TABLE 5.—*Influence of Single Administration of Fat on the Blood Sugar and Skin Sugar of Normal Rabbits*

	Rabbit 1			Rabbit 2		
	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio
Fasting.....	104	134	129	106	136	128
One hour after 2 cc. cod liver oil.....	106	130	123	108	130	120
Two hours after 2 cc. cod liver oil.....	108	124	115	110	126	115
Three hours after 2 cc. cod liver oil.....	112	120	107	108	122	113

TABLE 6.—*Influence of Repeated Administration of Fat on the Fasting Blood Sugar and Skin Sugar of Normal Rabbits*

	Rabbit 3			Rabbit 4		
	Fasting			Fasting		
	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio
On normal diet	100	134	134	107	138	129
On normal diet + 2 cc. cod liver oil daily for ten days.....	96	102	107	105	107	101

Finally we studied the influence of a low fat diet on the fasting blood sugar and skin sugar in man. Persons who adhered to the low fat regimen for five weeks showed a definitely higher blood sugar and skin sugar than when they were maintained on a low carbohydrate intake (table 7).

SUGAR CONTENT OF THE SKIN UNDER PATHOLOGIC CONDITIONS IN MAN AND IN ANIMALS

In diabetes mellitus the ratio between skin sugar and blood sugar shifts in favor of the skin. Thus we observed 7 diabetic patients who presented an average fasting blood sugar level

18. Adlersberg, P., and Porges, O.: Fettnahrung und Kohlehydrattoleranz, Med. Klin. **27**:1783, 1931.

19. Stolte, K.: Freie Diaet beim Diabetes (Erwiderungen auf die Ausfuehrungen des H. Prof. Carl v. Noorden), Med. Klin. **29**:288, 1933.

20. Hirsch-Kauffmann, H., and Knauer, H.: Ueber den Einfluss von Kohlehydrat- und Fettzufuhr auf Glykaemie und Lipoidstoffwechsel, Med. Klin. **29**:562, 1933.

21. Himsworth, H. P.: Influence of Diet on Sugar Tolerance of Healthy Men and Its Reference to Certain Extrinsic Factors, Clin. Sc. **1**:251, 1934.

22. Sikinami, Y., and Hosokawa, H.: Ueber die Hautzuckererhoehung und die Leberglykogenverminderung nach Fettbelastung, Tohoko J. Exper. Med. **35**: 257, 1939.

22a. Urbach, E., and Lentz, J. W.: Influence of High Fat Diet on the Skin Sugar in Rabbits. J. Invest. Dermat., to be published.

55 mg. per hundred cubic centimeters and a sugar level of 103 mg. per hundred grams—ation of 66.4 per cent.

The diabetic skin sugar curve in man (fig. shows certain typical peculiarities during tolerance test. The peak of the rise in etic patients is generally not reached in the until two hours have passed, and not well toward the end of the third hour as as the skin is concerned. Accordingly the sugar level is still high after four hours.

TABLE 7.—*Difference in Effect Between Low Fat and Low Carbohydrate Diets on Fasting Sugar of Blood and Skin*

Patient	Age	Sex	Disease	After Normal Diet			After Low Carbohydrate Diet			After Low Fat Diet		
				Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio
M	70	♂	Epithelioma	105	63.5	60	86.9	53.7	61.7	103.5	64.2	62
W	45	♀	Psoriasis	104.2	63.4	60.8	90.3	55.0	60.9	108	67.2	62.2
E	30	♂	Xanthoma	111.2	64.4	59.3	97.1	59.8	61.6	106	65.2	61.5

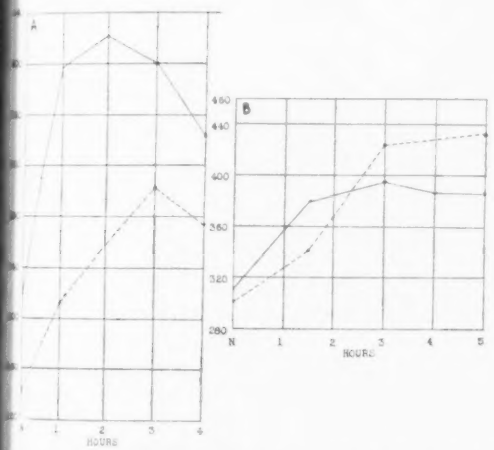

Fig. 4.—Influence of diabetes on sugar tolerance of n and blood. *A*, curves of persons with diabetes; *B*, rves for a dog one week after total pancreatectomy.

en in those cases in which the blood sugar s definitely begun to drop by this time. Therefore, the ratio skin sugar to blood sugar is most 80 per cent at the end of the fourth hour.

Even more pronounced are the disturbances in e course of the skin sugar curve in total pan-reatectomized dogs. Due in all probability to e complete deficiency of the pancreas, the in sugar rises uninterruptedly throughout the uration of the experiment and ultimately reaches finitely higher levels than does the blood sugar fig. 4 *B*).

However, persons with severe diabetes and tally pancreatectomized dogs unmistakably ow that the skin sugar curve, following administration of glucose, is just as dependent on the pancreas as the blood sugar curve has long been known to be.

Turning to cases of mild diabetes in man, it is necessary as far as fasting skin sugar levels are concerned to distinguish between two categories, namely those with and those without manifestations in the skin. In the former we include notably such manifestations as recurrent furunculosis, hidrosadenitis axillaris, eczema, urticaria and pruritus among cutaneous diseases of significance. Table 8 illustrates this fact. Patients with cutaneous manifestations while presenting only slightly increased fasting blood sugar show a high fasting skin sugar (average 82.8 mg. per hundred grams). On the other hand, those without cutaneous symptoms reveal only a slight elevation in skin sugar (average 65.5 mg. per hundred grams). Therefore the ratio of skin sugar to blood sugar is considerably higher in persons with mild diabetes with cutaneous manifestations (65.7 per cent) than in those without such manifestations (49.6 per cent).

TABLE 8.—*Skin: Blood Sugar Ratio in Relation to Skin Lesions in Persons with Mild Diabetes*

Skin Lesions Present			Skin Lesions Absent		
Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio Skin Sugar/ Blood Sugar, per Sent	Blood Sugar, Mg.	Skin Sugar, Mg.	Ratio Skin Sugar/ Blood Sugar, per Cent
125	95	77.9	127	69	54.3
129	95	73.6	130	67.5	51.9
117	80.5	68.8	132	62.5	49.3
117	78.5	67.5	135	62.5	46.3
125	74.5	59.6	143	66.2	46.2
118	67.9	57.2			
160	88.1	55			
Average:					
127	82.8	65.7	133	65.5	49.6

While the available material may seem inadequate, the possibility of mere coincidence in these findings appears to be precluded by the regularity with which the sharp rise in the skin sugar level in diabetic persons with cutaneous manifestations, on the one hand, and the absence of any abnormal increase in the skin sugar in those without cutaneous lesions, on the other

hand, could be demonstrated. However, further investigations on greater material will be necessary.

Interesting, too, are the results of studies we carried out on the behavior of the skin sugar following administration of insulin. When we gave animals insulin in doses large enough to bring on severe muscle spasm and death after two hours, we found that the skin sugar and blood sugar curves were fairly parallel, falling steeply at first, then dropping less precipitously. However, the skin sugar could not be depressed below a certain level, even when death was imminent. Thus, in dogs the sugar level dropped more than 50 per cent in the blood and approximately 40 per cent in the skin; in rabbits, close to 75 per cent in the blood and 63 per cent in the skin. Tsukada [17] arrived at similar results (76 per cent and 66 per cent).

BEHAVIOR OF THE SKIN AND BLOOD SUGAR IN VARIOUS DISEASES OF THE SKIN

On the basis of our material, we can divide the cutaneous conditions into six distinct groups:

(1) Cutaneous diseases in which the carbohydrate metabolism is in no way involved (skin sugar and blood sugar curves normal)

(2) Cutaneous diseases in frankly diabetic patient as evidenced by fasting hyperglycemia

(3) Dermatoses in persons with latent diabetes, in whom the nature of the disease can be demonstrated only by means of the sugar tolerance test

(4) Dermatoses in persons with normal fasting blood sugar but with high fasting skin sugar levels (cutaneous glycohistechia,[23] or skin diabetes)

(5) Skin diseases in persons who may present an atypical blood sugar curve, but who are nevertheless not diabetic, as demonstrated by the normal skin sugar curve

(6) Skin diseases which are not the result but the cause of increased blood and skin sugar levels, as demonstrated by the fact that both curves return to normal after the dermatosis has been cured by external therapy.

The first group is of no concern to us here. In the second group the blood and skin sugar curves show the typical diabetic contours previously mentioned and as exemplified in figure 5. The clinical manifestations include certain forms of eczema, as well as balanitis, pruritus, urticaria, staphylococcic diseases (folliculitis, furunculosis, carbuncles, pyoderma, hidrosadenitis axillaris), monilia infection of the skin, xanthosis, xanthoma, necrobiosis lipoidica diabeticorum and gangrene of the toes. Needless to say, only a small percentage of cases of these diseases is attributable to diabetes, except of necrobiosis lipoidica. However, that diabetic causation must always be borne in mind is shown by the statistics published by von Noorden and Isaac.[24] In their material, which consists of 25,000 diabetic persons, 21.5 per cent of the patients suffered from pruritus at one time or another; while in a group of patients over 50 years of age, from 5 per cent to 8 per cent presented refractory eczema and 10 per cent had furunculosis, carbuncles or acneform eruptions. According to Greenwood,[25] who studied the skin in 500 cases of diabetes at Dr. Joslin's clinic, diabetic patients show a higher incidence of infections of the skin than do nondiabetic persons. This is corroborated by the investigations of Pillsbury and Sternberg,[26] who demonstrated that the course of experimental cutaneous infections is much more severe in dogs on a high carbohydrate intake than in those on a low carbohydrate diet.

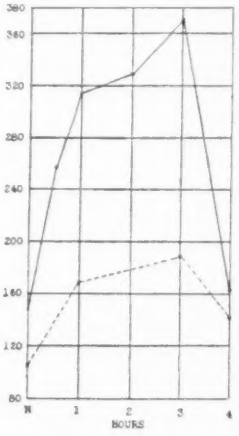

Fig. 5.—Diabetic sugar tolerance curves of blood and skin in a case of hidrosadenitis axillaris (complicating diabetes).

Group 3 comprises the cases in which the fasting blood and skin sugar appear normal, but in which sugar tolerance tests reveal a diabetic curve. The possibility of latent diabetes should always be borne in mind when the dermatosis presents unusual symptoms such as inordinate severity or extent (e. g., of an eczema or furunculosis), unusual localization (e. g., a dermatitis in the genital regions or in the intertriginous areas, fissures in the corners of the mouth or pruritus vulvae) or failure of the usual therapy.

23. (Greek: γλυκύς = sweet, ἱστίον = tissue, ἔχειν = to hold).

24. von Noorden, C. H., and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung, Berlin, Julius Springer, 1927.

25. Greenwood, A. M.: A Study of the Skin in Five Hundred Cases of Diabetes, J. A. M. A. **89**:774 (Sept. 3) 1927.

26. Pillsbury, D. M., and Sternberg, T. H.: Relation of Diet to Cutaneous Infection, Arch. Dermat. & Syph. **35**:893 (May) 1937.

...tic measures or when the clinical characters ... the patient (habitus, age, race) arouse sus... ...ion. Obese persons over 50 years of age, ... a somewhat purplish red complexion, are ...ten liable to have latent diabetes, especially ...ten they are of Jewish parentage.

As an example we present the case of an obese ...man of 32 who had been suffering from severe ...icaria for many months. The sugar tolerance, ...hile starting with normal blood and skin sugar ...alues (fig. 6), showed a typical diabetic re... ...onse. Elimination of carbohydrates from the ...et for twenty-four hours caused urticaria to ...disappear, while it reappeared three hours after ...three pieces of sugar had been taken in tea. ...The patient presented no manifestations so long ...as she adhered to a carbohydrate-free diet.

Similar circumstances have been encountered ...in a few cases of pruritus and eczema ani, furun... ...culosis, abscesses of the sweat glands, etc.

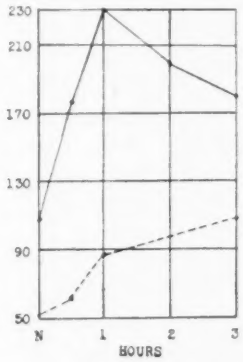

Fig. 6.—Latent type of sugar tolerance curve of blood and of skin in a case of urticaria in a subject with a prediabetic condition.

Group 4 comprises the relatively rare cases in which the blood sugar values are normal while the skin sugar level is well above the normal. This discrepancy becomes even greater following a sugar tolerance test, when the skin sugar curve alone becomes pathologic. One of us (E. U.)[2] has coined the term cutaneous glycohistechia, or skin diabetes, to designate this phenomenon. Further details of this interesting phenomenon will be presented in a study soon to be published.[27] For the present we shall limit ourselves to the statement that we should probably include in this group those cases reported by French authors in which insulin treatment was beneficial for refractory ulcers of the skin despite a normal blood sugar curve.

Group 5, on the other hand, comprises the dermatoses in which the sugar tolerance test shows an enormous rise in the blood sugar level, which returns to normal, however, after three hours. The skin sugar curve (fig. 7) in contrast to the blood sugar curve is normal in these cases. Table 9 clearly illustrates the difference between sympathetic-endocrine and diabetic skin sugar curves. In the former there is nothing like the excessive rise shown by the blood sugar curve; the peak is reached during the first hour, and the level returns to the normal between the third and fourth hours. The diabetic skin sugar curve shows considerably higher fasting levels to begin with; it does not reach its much higher peak, however, until the third hour; and takes five hours or more to return to its normal level.

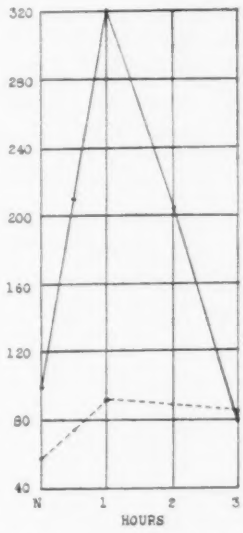

Fig. 7.—Sympathetic-endocrine blood sugar tolerance curve. Note the lack of parallel between skin and blood sugar curves.

TABLE 9.—*Difference Between Sympathetic-Endocrine and Diabetic Blood Sugar*

	Curves	
	Sympathetic-Endocrine	Diabetic
Time of peak....	30 to 60 minutes	2 to 3 hours
Shape of curve...	Sharp rise, steep fall	Flat with prolonged gradual decline
Return to starting level	In 2 to 3 hours	At least 4 hours
Hypoglycemia...	May occur	Does not occur

We encountered such atypical blood sugar curves notably in severe ulcera cruris, in a case of pyoderma chronicum ulcerosum, in several cases of urticaria and others. A common characteristic of these various diseases was their therapeutic refractoriness to a low carbohydrate diet, prolonged administration of insulin and local application of insulin to the ulcers. Therefore,

27. Urbach, E.: Skin Diabetes: Hyperglycodermia Without Hyperglycemia, J. A. M. A. **129**:438 (Oct. 6) 1945.

in conformity with the normal skin sugar curve after a sugar tolerance test, we feel justified in attributing these pathologic blood sugar curves not to a decrease in sugar tolerance but to an excessive mobilization of dextrose (Holsti [28]), probably of endocrine and/or sympathetic origin. This interpretation would also serve to explain the combination of fasting hyperglycemia and elevated basal metabolism or hyperglycemia during a sugar tolerance test, as observed in acne vulgaris by Levin and Kahn [29] as well as by Urbach.[30] This makes understandable McGlasson's [31] observation that patients with neurodermatitis with high blood sugar levels who failed to respond to a diabetic diet or to insulin were cured by a change of climate (in the mountains).

We consider it of great clinical significance that the patients in this group show no improvement whatsoever when put on a low carbohydrate diet and given a long course of treatment with insulin.

We now come to group 6. Disturbances of the carbohydrate metabolism, as evidenced by elevated fasting blood sugar and skin sugar levels and by pathologic blood sugar and skin sugar curves, and attributable to an extensive experimental dermatitis of chemical or mechanical origin, were first demonstrated by Miyake and associates.[32]

According to these authors, the blood sugar and skin sugar are affected because the severe inflammation of the skin leads to the formation of by-products, which either directly or by way of the nervous system affect the cells of the liver and thus bring about an insufficiency of the carbohydrate metabolism. Pillsbury and Kulchar [33] noted in animals that following an injection of dextrose the inflamed skin generally showed a higher sugar level than did normal skin areas.

The results of these animal experiments seem to conform perfectly with those obtained by Moncorps,[34] Milbradt [35] and Marchionini [36] in their studies of human material. Their investigations reveal that intensive ultraviolet irradiation is followed by a rise in the skin sugar and blood sugar levels and by pathoglycemic sugar tolerance curves.

Noteworthy in this connection are the observations reported by Ayres,[37] Schmidt,[38] Whitfield [39] and others to the effect that pyogenic infections decrease the patient's dextrose tolerance, or at least decrease the rate at which sugar is removed from the blood stream and the tissues. After the dermatosis has cleared up under suitable external treatment it is often found that the blood sugar level has returned to normal. In animal experiments Nicholson and Holman demonstrated that staphylococcal skin infection produced a definite although temporary decrease in carbohydrate tolerance in rabbits, with glucose tolerance curves similar to those seen in mild diabetes.

Similarly Moncorps and Speierer [41] found that in some of their patients with psoriasis who presented abnormal curves following administration of glucose the blood sugar level returned to normal after the eruption had cleared up.

We have been unable to confirm Panti's [41a] claim that in psoriasis the sugar content of the skin rises relatively more than does that of the blood.

In summary of this group it may be said, therefore, that in man and animals alike extensive inflammations of the skin can exert an influence on the carbohydrate metabolism; which

28. Holsti, O.: Studies Concerning Variations of Blood Sugar Reaction in Disease, Acta med. Scandinav. **66**:443, 1927.

29. Levin, O. L., and Kahn, M.: Biochemical Studies in Diseases of Skin: Acne Vulgaris, Am. J. M. Sc. **164**:379, 1922.

30. Urbach, E.: Untersuchungen ueber den Energiestoffwechsel bei Hautkranken, Arch. f. Dermat. u. Syph. **152**:304, 1926.

31. McGlasson, I. L.: Hyperglycemia as Etiologic Factor in Certain Dermatoses, Arch. Dermat. & Syph. **8**:665 (Nov.) 1923.

32. Miyake, I., and Narahara, K.: Eczematoese Hautveraenderung und Zuckerstoffwechsel: Hautzucker und eczematoese Hautveraenderung, Jap. J. Dermat. & Urol. **30**:85, 1930.

33. Pillsbury, D. M., and Kulchar, G. V.: The Dextrose and Water Content of Normal and of Inflamed Skin, Arch. Dermat. & Syph. **30**:489 (Oct.) 1934.

34. Moncorps, C.; Bohnstedt, R. M., and Schmid, R.: Ueber den Zucker- und Glutathiongehalt von Blut und Haut bei Hoehensonne-und Crotonoeldermatitis, Arch. f. Dermat. u. Syph. **169**:67, 1934.

35. Milbradt, W.: Der Einfluss der experimentellen Dermatitis auf den Funktionszustand innerer Organe, Arch. f. Dermat. u. Syph. **169**:494, 1934.

36. Marchionini, A.: Hautkrankheiten und Stoffwechsel, Med. Welt **11**:1197, 1937.

37. Ayres, S., Jr.: Glucose Tolerance Reactions in Eczema, Arch. Dermat. & Syph. **11**:623 (May) 1925.

38. Schmidt, E. G.; Eastland, J. S., and Burns, J. E.: Infection and Tolerance for Dextrose, Arch. Int. Med. **54**:466 (Sept.) 1934.

39. Whitfield, A.: Dermatoses and Nutrition, 9. Internat. Dermat. Cong. **1**:252, 1935.

40. Nicholson, T. F., and Holman, W. L.: Carbohydrate Metabolism and Staphylococcus Infection in Rabbits, Proc. Soc. Exper. Biol. & Med. **49**:75, 1942.

41. Moncorps, C., and Speierer C.: Psoriasis und Kohlehydratstoffwechsel, Arch. f. Dermat. u. Syph. **164**:642, 1932.

41a. Agostini, A., and Panti, A.: Piodermite necrotica con esito letate in soggetto ipoglicemico, Dermosifilografo **15**:242, 1940.

means, in other words, that this metabolic disturbance may fundamentally be of peripheral origin. As to the precise manner in which the periphery (e. g., the skin) exerts its influence on metabolism, whether this takes place as a result of an influx of nitrogen or uric acid released in the skin due to increased nuclear disintegration or indirectly via the endocrine glands or via the vegetative nervous system, very little is as yet known. However, some authors have derived substances from artificially inflamed skin which raise the blood sugar level and prolong the sugar tolerance curve. This would seem to demonstrate conclusively that the disturbances in the carbohydrate metabolism which appear in the course of transient dermatoses and disappear when the cutaneous manifestations clear up are in no way connected with pancreatic diabetes.

The practical conclusion to be drawn from these observations is that great care must be taken in evaluating the pathoglycemic results with regard to the pathogenesis and therapy of extensive or inflammatory diseases of the skin. For it is only when antidiabetic treatment (diet and or insulin) is followed by clinical improvement that the etiologic significance of the disturbance of the carbohydrate metabolism may be regarded as firmly established. Otherwise the metabolic disturbance should be interpreted as a result of the skin disease.

ROLE OF THE SKIN IN INTERMEDIARY CARBOHYDRATE METABOLISM

One of us (E. U.) has for years been championing the concept that the skin not only serves as a temporary storehouse of dextrose but also plays an important role in the intermediary carbohydrate metabolism. We submit the following evidence in support of this thesis: (1) the high levels of free and bound sugar in the skin of animals, (2) the demonstrable presence of cleavage and end products of the intermediary carbohydrate metabolism in the skin, (3) the skin's capacity to transform glucose into glycogen, (4) the presence of glycolytic ferments in the skin and (5) the fact that insulin-like substances can be derived from the skin.

(1) Urbach and associates [2, 5] were the first to demonstrate that the skin of almost all animals contains appreciably higher quantities of free sugar than does the blood. These findings have been confirmed by many other authors. Furthermore, human and animal skin shows bound sugar levels that are from ten to fifteen times higher than those of the blood (table 3).

Since the bound sugar is to be regarded as the organism's second sugar reserve (Grevenstuck,[42] Niwa [42]), the high levels in the skin would seem to be the expression not merely of a process of diffusion or of storage but of an active carbohydrate metabolism.

(2) Lactic acid is an important product in the intermediary metabolism of carbohydrates. It is of particular interest to note, therefore, that Fahrig [43] and Wohlgemuth and Ikebata [44] were able to demonstrate that the skin is capable of transforming dextrose into lactic acid in vitro. However, it was Pillsbury [45] who established the fact that lactic acid is present in the normal living skin, and that its lactic acid level tends to be low in starved animals and higher in well fed animals; and lastly, that the skin of animals previously given injections of dextrose forms increased amounts of lactic acid in vitro. These findings have been confirmed by Moncorps.[46] The quantitative fluctuations of the lactic acid in the skin thus serve as an index of the relative intensity of the carbohydrate metabolism in that tissue.

(3) The fact that investigation with special staining procedures reveals the glycogen in the epithelial sheaths of the hair follicle and in the sebaceous sweat glands, and nowhere else in the skin, is the reason why the presence of glycogen in the skin has long been disputed. Studies with quantitative chemical methods have, however, settled this controversy conclusively. Some time ago Palmer,[47] as well as Urbach and Sicher,[4] mentioned the rapid increase in skin sugar due to postmortem glycogenolysis—a statement inferring the presence of not inconsiderable amounts of glycogen. Fahrig [43] found glycogen values ranging between 226 and 344 mg. per hundred grams in the epidermis, and between 71 and 157 in the corium of the human skin. According to Cornbleet,[48] the skin normally contains from 68 to 85 per hundred grams of gly-

42. Niwa, Y.: Gebundener Zucker als Zuckerreserve, Kyto-Ikadaigaku-Zasshi **5**:25, 1931.

43. Fahrig, C.: Ueber den Kohlenhydratumsatz der Geschwuelste und ihrer normalen Vergleichsgewebe sowie seine Beziehung zum Milchsaeurehaushalt des Koerpers, Ztschr. f. Krebsforsch. **25**:146, 1927.

44. Wohlgemuth, J., and Ikebata, T.: Die Fermente der Haut: VIII. Ueber Milchsaeurebildung in der Haut und ihre Beeinflussung durch verschiedene Strahlenarten, Biochem. Ztschr. **186**:43, 1927.

45. Pillsbury, D. M.: The Intrinsic Carbohydrate Metabolism of the Skin, J. A. M. A. **96**:426 (Feb. 7) 1931.

46. Moncorps, C.: Kohlenhydratstoffwechsel und Haut, Jahresk. f. ärztl. Fortbild. **22**:27, 1931.

47. Palmer, W. W.: The Concentration of Dextrose in the Tissues of Normal and Diabetic Animals, J. Biol. Chem. **30**:79, 1917.

48. Cornbleet, T.: Cutaneous Carbohydrates, Arch. Dermat. & Syph. **41**:193 (Feb.) 1940.

cogen. Warren [49] adds the interesting observation that the skin of diabetic patients shows lower levels. Cornbleet [48] established the fact that, while phlorhizin poisoning lowers the dextrose levels in the blood and in the skin, it does not affect that of cutaneous glycogen. This shows, once again, that skin sugar and glycogen can be mutually independent. The Kaplanskys [50] demonstrated that the skin glycogen curve, following feeding of sugar, presents the direct reverse of the skin sugar curve. Moreover, as Cornbleet [48] has demonstrated, injection of insulin causes the skin's glycogen level to rise and that of the skin sugar to fall. The fact that the sugar concentration is higher in the skin than in the blood of animals is attributed by the Kaplanskys to the glycogenolysis that takes place in the skin. Furthermore, these authors are of the opinion that the rise in the skin's glycogen content, accompanied by a decline in skin sugar levels, may be explained by glycogen synthesis in the skin. The skin's high diastase level (130 to 170 mg. per hundred grams)—a level that almost approaches that of the liver—suggests the presence of enzymatic activity. On the other hand, Pillsbury and Sternberg [26] state that the glycogen level in the skin of dogs shows only a mild response to variations in the diet (129 mg. per hundred grams on a high carbohydrate diet, as compared with 107 mg. on a low carbohydrate diet). Narahara [51] observed that in contrast to the great fluctuations in the skin glucose levels following sugar administered by mouth, the skin glycogen levels remained relatively constant. This led Narahara to the conclusion that the skin plays an important role as a temporary receptacle for sugar, but that its role as an organ for permanent storage is rather small.

(4) To date the glycogenolytic and glucolytic enzymes which have been demonstrated in the skin consist in part of hydrolases (such as carbohydrases, amylases, diastases and glucosidases), which split up carbohydrates into simple cleavage products by means of hydrolysis; and desmolases (such as carboxylases, phosphatases, oxidation-reduction systems such as glutathione), which directly attack the carbon chain (Wohlgemuth and associates,[52] Melczer,[53] Morcorps [46]). Only a few of the most important findings will be selected from the great mass of pertinent reports. According to Wohlgemuth [52] the levels of starch-splitting ferment, diastase, are considerably higher in the skin than in the liver, sometimes even higher than in the blood. It is interesting to note that the skin of animals contains far more diastase than does human skin, which conforms perfectly with the relatively low skin sugar levels in animals. Ottenstein [54] established the fact that in diabetic persons the fasting blood shows low diastase levels, while they are strikingly high in the skin of the patients.

Wohlgemuth [52] and others demonstrated that the skin, as well as the liver and the muscles, form acetaldehyde from carbohydrates and that traces of acetaldehyde can be demonstrated in the freshly excised skin even when no sugar is added. The skin's participation in the oxidation of sugar as established by these investigations must not be underrated when viewed in contrast to the role played by the liver in this respect. For it must always be remembered that the skin is a much larger organ, being three times as heavy as the liver and constituting approximately 16 per cent of the total weight of the body. Wohlgemuth has further demonstrated that under suitable experimental conditions the skin is capable of converting phosphorylated sugar into methylglyoxal, and of transforming this in turn into lactic acid. Thus the sugar degradation process goes through the same stages in the skin as in the muscle and liver.

(5) Perutz, Lustig and Klein [55] demonstrated some time ago that the liver is not the only organ responsible for ketogenesis and the resulting ketosis, but that the skin also takes part in the process. Midana and Del Grande [56] were able to demonstrate the presence of abnormally high ketone levels in the blood of patients (on a carbo-

49. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1938.

50. Kaplansky, S. J., and Kaplanskaya-Rayskaya, S. J.: Carbohydrate Metabolism in the Skin, Arch. biol. Nauk. **39**:169, 1935.

51. Narahara, K.: Experimentelle Untersuchung ueber den Hautzucker: IX. Hautglykogen und Zuckerabbau in der Haut, Jap. J. Dermat. & Urol. (Abstr. Sect.) **35**:31, 1934.

52. Wohlgemuth, J.: Ueber den Kohlehydratstoffwechsel der Haut, Deutsche med. Wchnschr. **57**:[illegible] 1931.

53. Melczer, N.: Beitraege zur Kenntnis der Fermente der menschlichen Haut, Dermat. Ztschr. **49**:[illegible] 1927.

54. Ottenstein, B.: Untersuchungen ueber den Gehalt der Haut und des Blutes an diastatischem Ferment und dessen biochemische Bedeutung bei Hautkrankheiten, Hautdiastase bei Hautkrankheiten und bei Diabetes, Biochem. Ztschr. **240**:344 and 350, 1931.

55. Perutz, A.; Lustig, B., and Klein, A. E.: Zur zentralen Regulation des Fettstoffwechsels der Haut oberflaeche, Arch. f. Dermat. u. Syph. **70**:511, 1934.

56. Midana, A., and Del Grande, L.: Ueber den Einfluss der pathologischen Vorgaenge der Haut auf die experimentelle Hyperketonaemie, Arch. f. Dermat. u. Syph. **171**:208, 1935.

drate-free diet) who presented an extensive dermatosis but no signs of hepatic changes. The authors conclude, therefore, that the skin is capable of forming ketone bodies under certain pathologic conditions. In this process there is a greater increase in beta-hydroxybutyric acid and aceto-acetic acid. The degree of the increase is dependent on the extent of the cutaneous disease. When the latter improves the ketone level in the blood returns to normal.

Employing a modification of Collip's procedure for obtaining insulin, Moncorps [46] succeeded in deriving a substance from the skin which was found to have the capacity of lowering the blood sugar and skin sugar levels considerably, a substance which bears a close resemblance, at the very least, to insulin. These observations have been confirmed by Milbradt [57] and Reusch.[58] Moreover, Schwarzmann [59] has reported a similar depressing action on the blood sugar of an aqueous skin extract.

Lastly, the literature contains numerous reports on experimental studies, to the effect that the skin and blood sugar curves need not necessarily run parallel to each other: under certain circumstances they can be quite dissimilar, and sometimes even take opposite courses. Thus, one of us [4] observed, in studies on patients with diabetes and on depancreatized dogs, that the rise in cutaneous sugar is both higher and of longer duration than the rise in blood sugar. Urbach,[4] Trimble and Carey,[60] as well as Tsukada,[17] have demonstrated that fatal doses of insulin cause a greater fall in blood sugar than in skin sugar and that it is impossible to depress the skin sugar below a certain level. Similarly, diabetic patients who have been undergoing a long course of insulin therapy and who have at the same time been on a low carbohydrate diet, also show a greater decline in the blood sugar than in the skin sugar level.[4] Furthermore, Sellei and Spiera [61] claim that blockade of the reticuloendothelial system, by means of water-blue or gold salts, serves to lower the blood sugar level, while the skin sugar level is appreciably raised in this manner.

We should like to mention some further facts which show that the skin sugar, more or less independently of the blood sugar, is influenced by certain metabolic factors, a point which once again emphasizes the role of the cutaneous tissues in intermediary carbohydrate metabolism. Thus, Tsukada [17] observed that when rabbits are kept exclusively on a diet of oats they show a relatively higher degree of sugar tolerance, as expressed by the behavior of the skin sugar level; and that, on the other hand, a strict cabbage diet makes for a lower degree of tolerance in this respect. This may probably be explained by the fact that the oat diet makes the skin relatively more acid while the cabbage diet, on the other hand, tends to alkalize it. Lastly, Tsukada found that injections of insulin had definitely less effect on the skin sugar when the animal's diet was acidotic than when it was alkalotic; and that the difference actually went so far that following administration of insulin animals fed oats presented no hypoglycemic manifestations whatsoever, while animals on a cabbage diet responded with severe muscle spasms.

These various facts, which have been arrived at by means of investigations along chemical and biologic lines, clearly point to the probable presence of an intermediary carbohydrate metabolism in the skin; and would also seem to refute the assumption of Folin and associates [62] that a high skin sugar level is to be regarded merely as the result of passive diffusion.

COMMENT

In the past few years many authors have investigated the relations between diseases of the skin and carbohydrate metabolism, either by studying the fasting blood sugar levels or by performing blood sugar tolerance tests. Various results have been arrived at in the course of these investigations. Disregarding the question of dermatoses in diabetic patients for the moment, it may now be considered as an established fact that a disturbance of carbohydrate metabolism occurs in only a few cutaneous diseases: certain types of eczema (notably those localized in the intertriginous zones and in the areas surrounding the excretory orifices); staphylococcal diseases, including furunculosis, carbuncles, ecthyma, pyoderma; dermatomycoses (here again notably

57. Milbradt, W.: Ueber das antiallergische und antiinfectioese Prinzip im Hautextract, 9. Internat. Dermat. Cong. **1**:688, 1935.

58. Reusch, E.: Untersuchung ueber die Wirkung von Hautextrakten auf den Blutzuckerspiegel, Ztschr. f. d. ges. exper. Med. **105**:743, 1939.

59. Schwarzmann, J. S.: Mitteilungen ueber einen Extrakt aus lebender menschlicher Haut, Dermat. Wchnschr. **103**:1210, 1936.

60. Trimble, H. C., and Carey, B. W., Jr.: On the True Sugar Content of Skin and of Muscle in Diabetic and Non-Diabetic Persons, J. Biol. Chem. **90**:655, 1931.

61. Sellei, C., and Spiera, M.: Die Rolle der Haut im Kohlenhydratstoffwechsel, Biochem. Ztschr. **296**:83, 1938.

62. Folin, O.; Trimble, H. C., and Newman, L. H.: Distribution and Recovery of Glucose Injected into Animals, J. Biol. Chem. **75**:263, 1927.

those localized in the intertriginous zones); necrobiosis lipoidica; xanthosis; certain forms of xanthelasma; and, lastly, many cases of pruritus. It must always be borne in mind, however, that disturbances in the carbohydrate metabolism are not infrequently a result of pathologic changes in the skin.

As mentioned in the beginning of this paper, one of us (E. U.) has long supported the view that analysis of the blood alone cannot by any means afford a clear picture of the chemistry of healthy or diseased skin tissue; and that, on the other hand, a study of biopsy specimens is essential for this purpose. A similar view is held by Barát and Hetényi,[63] who were able to demonstrate that the blood sugar level does not in itself constitute a dependable index of the sugar retention in the muscle tissue of diabetic patients. Pollak [64] also pointed out that the blood sugar level does not by any means offer a guide for measuring the quantity of free dextrose which may temporarily be present in the organism. Furthermore, Barát and Hetényi [63] found in studies on corpses that the organs of diabetic and of nondiabetic persons could be differentiated by the higher sugar levels in the former; and that in cases of hyperglycemia of nondiabetic origin the tissue sugar levels were not abnormally elevated.

Similarly, Urbach and Sicher [4] established the fact in cases of so-called sympathetic endocrine hyperglycemia (fig. 7) that the skin sugar curve in no way takes part in this rise, an observation which further proves that the enormous rise in blood sugar level is not of diabetic origin.

It is true that the great rise in blood sugar which generally takes place during the sugar tolerance test in human beings or animals on a low carbohydrate diet is accompanied by a corresponding rise in the skin sugar levels; but both levels return to normal speedily, while they remain elevated for some time in diabetic subjects.

Lastly, there is the type of case which presents hyperglycoderma without hyperglycemia. In such cases the eruption does not yield to therapy until the patient is put on an antidiabetic diet.

It is, therefore, essential to carry out determinations of the skin sugar in all doubtful cases in which the presenting cutaneous disease might possibly be attributable to a disturbance in the carbohydrate metabolism. We call this method "chemical biopsy" of the skin. While it has b demonstrated again and again that certain der toses are the consequence of a disturbance the carbohydrate metabolism, the nature of pathogenesis involved is still a highly con versial question. The following more or well founded theories have been advanced explain the connection:

(1) The increased concentrations of sugar, of an intermediary product of the carbohydra in the skin act in one of three ways: by dir stimulation of the sensory nerves of the sk causing pruritus; by creating a disturbance the secretory and vasomotor nerves, resulting anhydrosis, asteatosis and xerosis of the sk or by exerting a direct influence on the capilla walls and glands (Kaposi).[64]

(2) J. Jadassohn [65] regards some of the cu neous diseases in diabetic patients as belong to the group of excretory dermatoses, on t theory that the sugar passing through the secr ing glands exerts a pathogenetic influence on t skin's bacterial flora. Carrie and Koenig [66] ha demonstrated that patients with high blood sug levels excrete abnormally large amounts of sug onto the skin surface.

(3) Abnormal decomposition products sugar bring about an "Umstimmung" (tran formation of the terrain) as a result of wh the skin reacts to endogenous and exogen stimuli other than those derived from the a normal sugar metabolism, with cutaneous ma festations (Bloch,[67] Achard [68]).

(4) According to Stokes, Beerman an Ingraham [69] ingested carbohydrate may influ ence infections of the skin through its action the bacterial content of the intestinal tract, cau ing vasomotor instability which constitutes clinically important factor predisposing to a wi variety of inflammatory reactions.

(5) The influence of carbohydrate on infe tions of the skin may be exerted through t effect on the water balance of the tissues. Fo a high carbohydrate intake leads to retenti

63. Barát, I., and Hetényi, G.: Zuckerbestimmungen im menschlichen Blut und Gewebe bei Diabetikern, Deutsches Arch. f. klin. Med. **141**:358, 1922-1923.

64. Pollak, L.: Physiologie und Pathologie der Blutzuckerregulation, Ergebn. d. inn. Med. **23**:337, 1923.

65. Jadassohn, J.: Hautkrankheiten bei Stoffwechsel anomalien, 5. Internat. Dermat. Cong. **2**:155, 1905.

66. Carrie, C., and Koenig, R.: Ueber den Zuckergehalt auf der Haut bei Normalen und Diabetikern, Arch. f. Dermat. u. Syph. **173**:611, 1936.

67. Bloch, B.: Beziehungen zwischen Hautkrankheiten und Stoffwechselanomalien, Ergebn. d. inn. Med. **2**:521, 1908.

68. Achard, C.: Cinque lecons sur le diabete, Paris, Masson & Cie, 1925.

69. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Carbohydrate and Water Metabolism and the Vitamins in Skin Inflammation, Am. J. M. Sc. **195**:582, 1938.

water in the tissues (Pillsbury and Sternberg),[29] while carbohydrate restriction results in dehydration followed by decreased susceptibility to experimentally induced cutaneous infections (Kulchar and Alderson [70]).

(6) Rudy and Hoffmann [71] champion the theory that cutaneous manifestations in diabetes mellitus are not related to the hyperglycemia but attributable to the skin's increased vulnerability resulting from a deficiency in the components of the vitamin B complex, notably nicotinic acid. These authors, as well as Gross,[72] report that lesions of the skin, including those of monilia infections in persons with diabetes, respond to treatment with vitamin B complex in addition to nicotinamide. However, since Neuwahl [73] has demonstrated that nicotinic acid improves the carbohydrate tolerance of diabetic patients and may enhance the action of insulin, the therapeutic effect of nicotinic acid—and therefore, of course, the explanation based on this effect—may not quite conform with Rudy and Hoffmann's views on the subject.

(7) Disorders of the skin involving extensive dermatitis of chemical or mechanical origin may bring on a disturbance in the carbohydrate metabolism. This is generally interpreted as evidence of injury to the liver, rather than as a sign of disturbed pancreatic function (Milbradt [35]).

(8) Lastly, Whitfield [39] alludes to the assumption that in many bacterial infections the thyroid-adrenal apparatus is brought into action as a part of the organism's defense mechanism. The resulting rise in the blood sugar is, therefore, an effect and not the cause of the cutaneous disease.

SUMMARY

Chemical analysis of the blood does not in itself suffice to give a clear insight into the physiologic and pathologic mechanism of the skin. For this purpose the living skin must be subjected to a chemical investigation. This can readily be done by means of the electric punch biopsy method; and corresponding microchemical methods now make it possible to undertake a series of biopsies.

While in human beings the free sugar content of the skin is only two thirds of that of the blood, the skin of many species of animals contains more free sugar than does their blood. Therefore results obtained in experimental investigations on animal skin are not automatically applicable to conditions in human beings.

The bound sugar content of the skin in human beings is about one and one half times that of the blood.

The sugar level of the skin is dependent on the nature of the diet. The same is true, although to a lesser extent, of the blood sugar. The individual who has been on a low carbohydrate diet shows definitely subnormal skin sugar levels, and he may well show low blood sugar levels as well. This fact clearly explains the efficacy of a low carbohydrate diet in diabetic dermatoses. It is interesting to note that the mean blood sugar and skin sugar levels in Philadelphians are lower than those in Viennese, whose diet is much higher in carbohydrate than the usual American diet.

A diet high in fat results in a distinct decrease in the sugar content of the skin while that of the blood remains practically stationary.

A blood sugar tolerance test is indispensable in order to answer the question whether or not a given dermatosis is of diabetic origin. However, the type of curve resulting indicates whether a given pathologic reaction is brought on by excessive mobilization of glucose by an imbalance in the sympathetic or the endocrine system, or by a decrease in the capacity to assimilate sugar, i. e. by a lowered sugar tolerance, as in diabetes.

Under normal conditions there is a certain parallelism between the skin sugar and the blood sugar tolerance curves with the one difference that the skin sugar curve reaches its maximum later and, correspondingly, takes longer to return to its original level.

Under pathologic conditions the skin is capable of containing more sugar and for a longer period of time, a fact which seems highly significant when one recalls that the skin constitutes 16 per cent of the total weight of the body and that the skin is three times as heavy as the liver.

In cases of pancreatic diabetes the ratio between the fasting skin sugar and the blood sugar is increased. Moreover, the sugar content of the skin is almost doubled after a sugar tolerance test. Lastly, it takes the skin sugar level five hours or even longer to return to normal. This gives the diabetic skin sugar curve its unmistakably characteristic appearance. The

70. Kulchar, G. V., and Alderson, H. E.: Relation of Water Metabolism to Experimental Skin Infections, Brit. J. Dermat. **48**:477, 1936.

71. Rudy, A., and Hoffmann, R.: Skin Disturbances in Diabetes Mellitus: Their Relation to Vitamin Deficiencies, New England J. Med. **227**:893, 1942.

72. Gross, P.: Nonpellagrous Eruptions Due to Deficiency of Vitamin B Complex, Arch. Dermat. & Syph. **43**:504 (March) 1941.

73. Neuwahl, F. J.: Action of Nicotinic Acid on Carbohydrate Metabolism, Lancet **2**:348, 1943.

prolonged and intensive storage of sugar in the skin may, perhaps, explain its great susceptibility to infection in diabetes. In mild diabetes with cutaneous manifestations the ratio of skin sugar to blood sugar is relatively high (65.7 per cent), whereas the ratio is rather low is cases without cutaneous symptoms.

Extensive inflammation or infection of the skin can produce a metabolic disturbance of the carbohydrate metabolism which is fundamentally of peripheral origin and in no way connected with pancreatic diabetes.

Under certain conditions there can be hyperglycoderma without hyperglycemia (cutaneous glycohistechia or cutaneous diabetes).

These facts together with the demonstrable presence of cleavage and end products of the intermediary carbohydrate metabolism in the skin, as well as the presence of glycolytic enzymes in the skin and the fact that insulin-like substances can be derived from cutaneous tissue would seem to underscore the important role played by the skin both in intermediary carbohydrate metabolism and as a storage organ.

EPIDERMOLYSIS BULLOSA

A SUGGESTION AS TO POSSIBLE CAUSATION

CAPTAIN MARVIN N. WINER AND CAPTAIN JACK MORTON ORMAN
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Epidermolysis bullosa, a comparatively rare dermatosis, was first recognized as an entity in 1879 by Tilbury Fox.[1] Goldscheider,[2] three years later, gave it the name it bears at the present time. Since then most observers have classified the disease into two main groups, namely the simple and the dystrophic forms. The simple form is characterized by the appearance of bullae on the skin, usually without changes in other ectodermal structures such as the teeth, hair and nails, whereas the changes in these appendages is the predominant feature of the dystrophic form. The dystrophic form of the disease has been further subdivided into two types based on hereditary transmission, as a dominant or as a recessive characteristic. Clinically, the dominant dystrophic type is intermediate in severity between the simple and the recessive dystrophic type. The nails may be thickened, clawlike, or absent, but as a rule the teeth and hair are sound, as is the general health of the affected person. In the recessive dystrophic type, on the other hand, severe abnormalities of all the ectodermal structures are evident, lesions of the mucous membranes are frequent since slight trauma will produce them, and the constitutional state of the victims is such that they seldom attain maturity.

The existence of a nonhereditary form of the disease was recognized as early as 1895.[3] In 1915 in an excellent review of the subject Wise and Lautman [4] summarized the literature and bibliography to that date, citing cases collected from the literature, along with 1 of their own, in most of which symptoms were not evidenced until a comparatively late age. Within recent years, Hundley and Smith,[5] Franks and Davis,[6] and Waisman [7] have reported cases corroborating the existence of an acquired type of the disease.

While epidermolysis bullosa is a comparatively rare entity, we believe a somewhat higher incidence is to be expected among military personnel. This is due to several factors: the increased susceptibility of soldiers to trauma, particularly that caused by prolonged marching, and the fact that many minor illnesses, often ignored in civil life, are promptly brought to the attention of medical officers. Greenberg [8] observed 5 cases of epidermolysis bullosa in a total of 2,281 cases seen on the Dermatologic Service at Camp Croft, South Carolina. It is partly to focus attention on this condition that we present the following case.

REPORT OF A CASE

A Negro private, aged 33, was admitted to the hospital on July 18, 1944 because of recurrent blisters on the right sole. These blisters were first noticed by the patient two years previously following prolonged walking, were subject to exacerbations and were most severe during the warmer months of the year. The bullae were moderately painful only on the first day or two following their appearance, and there was no pruritus. A moderate hyperhidrosis was sometimes evident.

The previous medical history was noncontributory with the exception of hospitalization for previous atypical pneumonia in April 1943. Despite a careful investigation of the family unit, no history of any similar bullous or vesicular lesions in any other member could be elicited, nor was there consanguinity of the parents.

On the plantar surface of the right foot there were numerous discrete, nonerythematous vesicles and bullae, varying in size from approximately 0.4 cm. to 1.2 cm. The lesions were predominantly located on the weight-bearing surfaces of the foot, the metatarsal area and the large toe; they were unilocular, thin-walled, only mildly tender and filled with a clear, thin, yellowish, serous

1. Fox, T.: Notes on Unusual or Rare Forms of Skin Disease: IV. Congenital Ulceration of the Skin (Two Cases) with Pemphigus Eruption and Arrest of Development Generally, Lancet **1:** 766, 1879.

2. Goldscheider, A.: Hereditäre Neigung zur Blasenbildung, Monatsh. f. prakt. Dermat. **1:** 163, 1882.

3. Elliot, G. T.: Two Cases of Epidermolysis Bullosa, J. Cutan. & Genito-Urin. Dis. **13:** 10, 1895.

4. Wise, F., and Lautman, M. F.: Epidermolysis Bullosa Beginning in Adult Life: The Acquired Form of the Disease, with the Report of a Case and Review of the Literature, J. Cutan. Dis. **33:** 44 (June) 1915.

5. Hundley, J. L., and Smith, D. C.: Epidermolysis Bullosa Acquisita, South. M. J. **34:**36, 1941.

6. Franks, A. G., and Davis, M. I. J.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **47:** 647 (May) 1943.

7. Waisman, M.: Recurrent Bullous Eruption of Feet and Hands (Weber-Cockayne): Localized Epidermolysis Bullosa, J. A. M. A. **124:** 1247 (April 29) 1944.

8. Greenberg, S. T.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **49:** 333 (May) 1944.

fluid. Nikolsky's sign was negative. At the site of previous lesions there was a mild hyperpigmentation, but no atrophy. No gross abnormalities of the hair or teeth were present. The nail of the large toe showed moderate hypertrophy with accumulation of brown corneous material beneath it; but no pitting, longitudinal striation or onychogryphosis was found. The fourth and fifth toes showed similar changes of a lesser degree, but all of these findings in the nails were interpreted as being consistent with the normal in persons of this race and status. At no time were any lesions discoverable elsewhere, and the mucous membranes were clear. The general medical examination gave negative results. Examination of the lower extremities revealed no gross abnormalities other than cutaneous changes. Although no definite measurements of the length of the extremities were taken, the examiners felt that no discrepancies were evident. Varicosities were neither visible nor palpable. The dorsalis pedis and posterior tibial arteries were easily felt, and were of normal consistency. No changes in temperature at any level of the extremities were noted. Repeated urinalysis and blood counts were normal, the basal metabolic rate was + 5 per cent and the blood calcium 9.4 mg. per hundred cubic centimeters. Several Kahn tests were negative. On six different occasions, examinations of the bullae did not reveal fungi, and repeated cultures of the bullous fluid failed to show a growth. The trichophytin test was also negative.

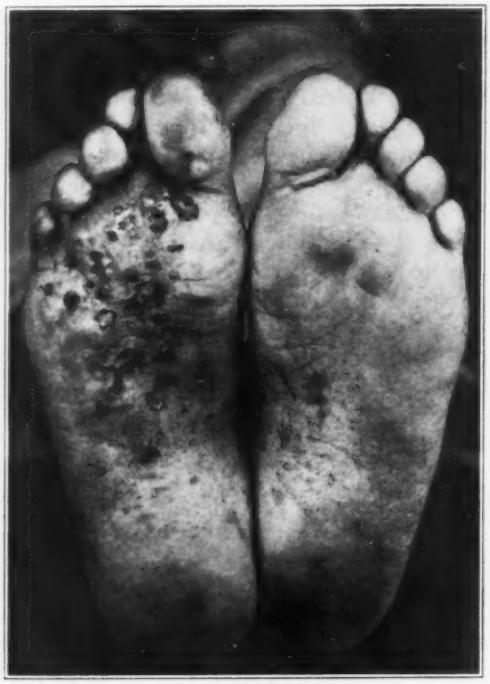

Fig. 1.—Epidermolysis bullosa. (Photographed by Army Air Forces.)

Histopathologic Description.—The section showed mild hyperkeratosis and a minimal degree of parakeratosis. The stratum corneum, containing ill defined vesicles, was separated from the granular layer by a vacuolar process. In the central portion of the slide there was a large epidermic cyst extending from the granular layer to the basal layer of the epidermis. The cyst was partially filled with fibrinous material and a few lymphocytes. In the lower central margin of the epidermic cyst there was a break in the continuity with liberation of a cellular infiltrate, consisting mostly of lymphocytes and monocleated cells, and an attempt at blood vessel formation. In the upper part of the corium there was a moderate inflammatory reaction consisting chiefly of lymphocytes, plasma cells and mononucleated cells. The infiltrate was predominantly localized around dilated blood vessels and extended into the papillae. There was some disorganization of the connective tissue elements in the corium with a tendency to separation of the fibers, with vacuolation.

ETIOLOGIC CONCEPTS

There have been many and divergent theories put forth in an attempt to explain satisfactorily the cause of this disease. Whether there is a common etiologic basis for the acquired and the hereditary forms has been the subject of considerable discussion and doubt. The concomitant presence of hyperhidrosis in some of these cases often has been considered of etiologic significance; however, in many instances excessive sweating is not seen, and certainly in our case hyperhidrosis was a symptom of relatively little importance. It seems more likely that this symptom is a secondary manifestation, an effect of the disease rather than the cause. It would be of interest in this regard to determine accurately whether the so-called hyperhidrosis that is allegedly frequently associated with epidermolysis bullosa is a true hyperhidrosis. Is it a true excess secretion of the coil glands or is it merely a diffuse leakage of serum through inherently defective cutaneous vessels? Studies of acidity of the fluid might be helpful. An endocrine basis for the disease has been advanced by some authors, with almost every ductless gland implicated by one observer or another. Pasini,[9] Drouet,[10] Bonaduce[11] and Kaftan[12] have implicated a thyroid dysfunction as responsible. Longo,[13] Stühmer[14] and Marcozzi[15] believed

9. Pasini, A.: Epidermolisi congenita bollosa e albo-papuloide, Gior. ital. di. dermat. e sif. **73**:125, 193

10. Drouet, L.: Endocrinides cutanées (sclérodermie, épidermolyse bulleuse) chez un myxoedémateux, Bull. Soc. franç. de dermat. et syph. **35**:503, 1928.

11. Bonaduce, F.: Osservazioni comparative sopra diversi casi di pemfigo traumatico congenito ed infantile, Gior. ital. di dermat. e sif. **67**:761, 1926.

12. Kaftan, F.: Ein Fall der Epidermolysis bullosa hereditaria mit typischen Erscheinungen im Munde und an den Zähnen, Deutsche Monatschr. f. Zahn. **43**: 165, 1925.

13. Longo, P.: Distrofia cronica della pelle a tipo di epidermolisi bollosa, Arch. ital. di dermat. e sif. **2**:449, 1927.

14. Stühmer, A.: Ueber Epidermolysis bullosa congenita (Dystrophia cutis spinalis congenita), Arch. f. Dermat. u. Syph. **121**: 568, 1918-1919.

15. Marcozzi, A.: Epidermolisi bollosa distrofica con ematoporfirinuria ed alterazione endocrinosimpatica, Arch. ital. di dermat. e sif. **4**:555, 1929.

combination of thyroid and suprarenal imbalance played an important part, while Hudelo and Moutlour [16] and Beinhauer [17] have implicated the gonads. Schwartz and Levin [18] presented 1 case in which the disease seemed to improve following the administration of parathyroid extract and calcium lactate. Association of porphyria and epidermolysis has been noted, but the work of Turner and Obermayer [19] discounted this factor as being of etiologic significance. The suggestion that allergy played a role was made by Ludy, Devalin and Drant,[20] who noted a lessened tendency to formation of bullae in 2 cases, after elimination of certain articles of diet. The experiments were not controlled nor was sufficient observation made over a long enough period for these authors to advance any definite theory.

application of chronic acid to the skin at sites of predilection. It is well known that chromic acid is one of the more frequent sensitizing agents in the pathogenesis of shoe leather dermatitis. Since Luithlen does not mention the concentration of chromic acid used to elicit this phenomenon, it is more than likely that he was dealing with primary irritation rather than true sensitization, and that the same phenomenon could occur in cases other than epidermolysis bullosa. Hemolytic streptococci, group G Lancefield, were isolated from bullae and found to be pathogenic for mice by Cannon, Sanders and Rankin.[22] This organism was isolated by these authors in almost pure culture from the lesions in 4 cases, and their patients showed definite clinical improvement with administration of sulfanilamide, locally and by mouth. It is our impression,

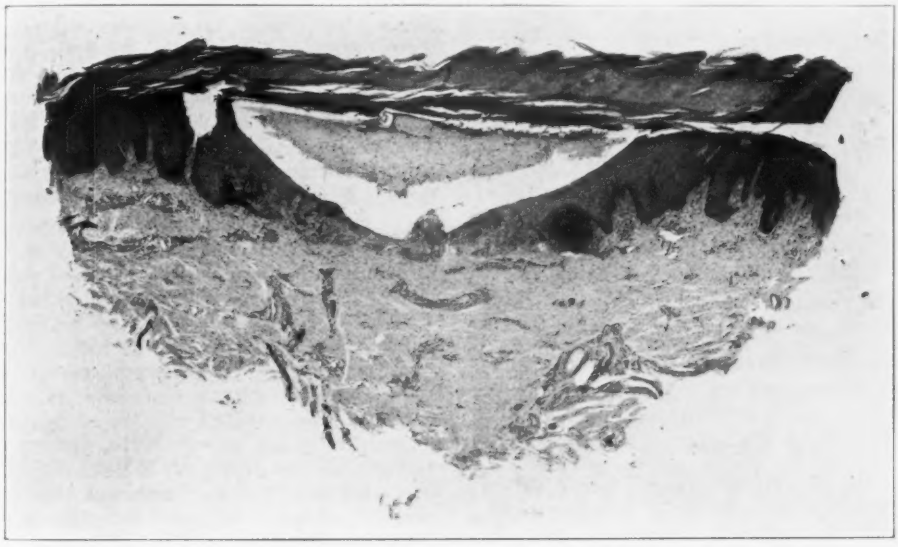

Fig. 2.—Epidermolysis bullosa. (Photographed by U. S. Army Medical Museum.) × 16.

It is of interest that in cases of epidermolysis bullosa showing primarily lesions of the feet that Luithlen [21] mentions the artificial production of bullae in epidermolysis bullosa by the

however, that the cultures in these cases were due to a secondary infection, since no subsequent reports have been published to our knowledge and since various bacteria have been cultured from both normal and abnormal skin.

A congenital absence of elastic tissue was found in histologic studies made by Engman and Mook.[23] They found a definite deficiency

16. Hudelo and Moutlour, cited by Petges, G., and Lecoulant, P., in Darier, J., and others: Nouvelle pratique dermatologie, Paris, Masson & Cie, 1936, vol. 6.

17. Beinhauer, L. G.: Treatment of Epidermolysis Bullosa, Arch. Dermat. & Syph. **32:** 469 (Sept.) 1935.

18. Schwartz and Levin, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

19. Turner, W. J., and Obermayer, M. E.: Studies on Porphyria: II. Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, Arch. Dermat. & Syph. **37:** 549 (April) 1938.

20. Ludy, J. B.; Devalin, C. M., and Drant, P.: Epidermolysis Bullosa, M. Clin. North America **16:** 169, 1932.

21. Luithlen, F.: Epidermolysis Bullosa Hereditaria, in Mracek, S.: Handbuch der Hautkrankheiten, Vienna, A. Hölder, 1902, vol. 7, p. 738.

22. Cannon, A. B.; Sanders, M., and Rankin, J. L., Jr.: Epidermolysis Bullosa; A Clinical and Bacteriologic Study; Report of Four Cases, Arch. Dermat. & Syph. **42:** 884 (Nov.) 1940.

23. Engman, M. F., and Mook, W. H.: A Study of Some Cases of Epidermolysis Bullosa, with Remarks upon the Congenital Absence of Elastic Tissue, J. Cutan. Dis. **24:** 55, 1906.

of elastic tissue in the papillary and subpapillary layers of the cutis, not only in the area affected by bullous lesions but also in regions apparently normal. On the basis of their findings it was suggested that there occurred a leakage of serum and the production of bullae due to separation of the cutis from the epidermis, at the most vulnerable portions. They believed that this diminution of elastic fibers accounted for the increased susceptibility of these patients to trauma. According to Wise and Lautman,[4] however, the uninjured skin was found to be normal in a case of the acquired type of the disease.

There is considerable substantiation in dermatologic literature for the theory that some disturbance of the vascular system underlies the disease. Whether this disturbance is in the nature of an actual structural change of vascular endothelium or whether it is due to some autonomic nervous imbalance has only been theorized, but in either case many observers have stated their belief that increased permeability of vessel walls occurs with transudation of serum into the upper part of the epidermis, with consequent production of bullae. Elliot[3] states that the prime feature in the pathogenesis of epidermolysis bullosa rests in "an acquired or hereditarily exaggerated irritability of the cutaneous vascular system," a belief which was also shared by Unna[24] and Török.[25]

With the theory of a basic disturbance of the cutaneous-vascular system in mind, several experimental procedures were attempted with our patient.

METHOD

(1) On July 24, 1944 an area of normal skin 1.5 inches (3.18 cm.) wide on the medial plantar surface of the right foot was moderately traumatized by stroking with the dull end of a curet for thirty seconds. The area was encircled with white photo ink. No lesions were seen to appear in this area within an observation period of forty-eight hours. On July 26 greater trauma was inflicted on the same area by a steady stroking lasting thirty seconds, followed by an interruption of thirty seconds, the entire cycle being repeated twenty-four times. Again, after a forty-eight hour period of observation no bullae were seen.

(2) On July 28, 0.1 cc. of a triple typhoid vaccine (containing one billion organisms of Bacillus typhosus and two hundred and fifty million organisms each of the paratyphoid bacilli A and B per cubic centimeter) was given intravenously. Three and one-half hours later the patient exhibited his most decided temperature response, 101.6 F. (oral). At this point, the preceding traumatizing procedures with the dull end of a curet were repeated, again with negative results.

(3) Beginning on July 31 the patient was allowed to walk for varying periods of time, under close supervision of a ward attendant, and it was determined that the minimal threshold time for the appearance of bullae was ten minutes. That is, after shorter periods of walking no lesions were found, but after walking for ten minutes from 7 to 8 bullae appeared on the original site after twenty-four hours. This threshold time was verified on several trials.

(4) On August 10 the patient was instructed to stand and rock backward and forward on the heels and toes of both feet. This was done one hundred times, with each forward and backward motion lasting two seconds. After twenty-four hours five new bullous lesions appeared on the ball of the right foot and on the plantar surface of the right large toe.

(5) On August 15, with the threshold time for the appearance of lesions determined and verified as being ten minutes, we attempted to see what proportion of the symptoms was dependent on autonomic nervous factors. The patient was given intravenously 7½ grains (0.49 Gm.) of sodium amytal in 10 cc. of sterile distilled water, by Capt. George Jervis, base psychiatrist. Seven minutes after the injection had been completed the patient was under mild to moderate narcosis. He was then supported lightly under each arm and instructed to walk for ten minutes. Twenty-four hours following this procedure five bullae were noted on the right sole. Incidentally, while the patient was narcotized an attempt to elicit any possible psychogenic factors was made by Captain Jervis, with completely negative results.

(6) On August 18 a tourniquet was applied below the right knee with moderate pressure. As it was impossible to determine accurately the amount of pressure used, and as the pressure was of the approximate degree one would use in applying a tourniquet for the purpose of withdrawing blood from the cubital vein in the arm, we felt that the pressure was exerted on the venous system primarily. Under observation by a ward attendant, the patient walked with the tourniquet intact for a period of fifteen minutes. The tourniquet was then removed and the patient put to bed. After twenty-four hours not a single new lesion was seen on the foot. On the following day this procedure was repeated. This time the patient walked for twenty minutes, and in place of the tourniquet an elastic bandage was applied from the right ankle to the knee. Again no lesions were seen twenty-four hours following removal of the bandage and placing the patient in bed.

(7) On August 20 the elastic bandage was reapplied and continuously left in place for three days. The patient was instructed to be up and about. The bandage was then removed and the patient returned to strict rest in bed. Despite considerable walking during the three day period that he wore the bandage, only one vesicle appeared on the plantar surface of the fifth right toe.

(8) On August 25 the patient was allowed to walk around the ward during the entire day without the elastic bandage in place. On the next day eight new vesiculobullous lesions were seen.

(9) To allow for possible factors of chance and coincidence, for eighteen consecutive days the patient walked freely about the ward, one day with the elastic bandage in place and the next day without it. On each of these trials the results were exactly the same. That is, no new lesions were seen after each day's walking with the bandage applied, whereas new lesions, usually num-

24. Unna, P. G.: Ueber die Duhringsche Krankheit und eine neue Form derselben, Dermat. Wchnschr. **9**: 97, 1889.

25. Török, L.: Epidermolysis hereditaria bullosa (Koebner), Arch. f. Dermat. u. Syph. **47**: 402, 1889.

during six to eight, appeared the day after he had walked without wearing the bandage.

(10) After allowing for partial involution of lesions and encircling any present with white photo ink, on October 3 the patient was made to wear the bandage continuously for a period of one week. During this period he had complete freedom of the ward. Despite considerable walking during this one week interval, only two lesions appeared at the end of this time.

(11) As a final check the elastic bandage was removed, and on October 10 the patient was allowed to walk freely again. Daily observation for a period of five days failed to reveal any new lesions. This was the first finding that was inconsistent with the previous ones. It may be noted, however, that the mean temperature for this five day period was only 59.8 F., whereas the mean temperature for the period in which the foregoing procedures were done averaged 73.5 F., a difference of 13.7.[26] It is well known that the incidence of bullae formation in epidermolysis bullosa decreases greatly during the colder months of the year. No further observations could be made since the patient was subsequently given a medical discharge from the service.

COMMENT

On analysis of these findings it was seen that with the wearing of an occlusive bandage, such as an elastic bandage or a tourniquet exerting only moderate pressure, the threshold of blister formation was considerably increased. Luithlen,[21] in his "Handbuch der Hautkrankheiten," observed that if one uses an Esmarck bandage to empty the extremity of blood no production of bullae results until the bandage is removed. This tends to support the contention of Elliot [3] that there is an underlying disturbance of the cutaneous vascular system in the pathogenesis of the disease. Where, however, is the original site of the disturbance? Engman and Mock [23] believed that a lack or scarcity of elastic tissue in the papillary and subpapillary layers of the cutis brought about a leakage of serum with the production of bullae in areas exposed to trauma. But, as Wise and Lautman [4] have shown, no deficiency of elastic tissue occurs in normal areas of skin of patients with epidermolysis bullosa.

Can the primary disturbance be due to an altered control of vascular tone by the autonomic nervous system, with attendant transudation of serum? It is beyond the scope of this paper to rule out all the factors which might cause an autonomic imbalance. An attempt was made, however, to determine whether some psychogenic factor played a part. This was suggested by the work of Goldman, Nelson and Mirsky,[27] who found that under pentobarbital sodium anesthesia the skin of ducks was much less susceptible to the production of vesicles by mustard agent. In our patient, however, one induction of narcosis by sodium amytal was completely ineffectual and no significant psychogenic factors could be elicited by a competent psychiatrist.

It is our impression, gained on the basis of observations in the case presented, that some inherent defect of the vessel wall itself may constitute the primary cause of epidermolysis bullosa, at least in the acquired form of the disease. Whether this likewise applies in the hereditary form is purely speculative, but it seems a not unlikely possibility. This inherent defect must be of such nature that no clinical signs of any vascular deficiency are ordinarily manifested. The added factor of muscular exercise, however, is sufficient to provoke the production of bullous lesions. In some manner, which we are not prepared to explain, the application of a tourniquet or elastic bandage must overcome the defect present and prevent the appearance of lesions. It appears that artificial trauma, with resultant transitory hyperemia, is not analogous to the muscular action of walking, for stroking with a blunt instrument did not produce bullae in our patient.

We should like to suggest that further vascular studies be carried out in cases of epidermolysis bullosa in an attempt to determine the site and mechanism of the underlying pathologic condition. Study of venous pressures, infra-red photography, venograms and biopsies of the vascular tree might contribute much to the knowledge of the pathogenesis of this condition.

SUMMARY

1. A case of simple acquired epidermolysis bullosa in a Negro is presented.

2. Corroborative evidence is brought forth for the theory that some defect of the vascular mechanism is primarily responsible for the manifestations of the disease.

3. It is shown that a diminished tendency to blister formation is achieved through the use of compressive bandages.

4. A plea is made for further experimental studies of the vascular system in this disease.

26. Army Air Force Base Weather Station, Barksdale Field, Louisiana.

27. Goldman, L.; Nelson, N., and Mirsky, A. I.: Production of Bullae in the Skin of the Duck: II. Experiments with Bullae Produced by Vesicants, Arch. Dermat. & Syph. **48**:616 (Dec.) 1943.

ACNE VULGARIS OCCURRING IN THE TROPICS IN A PIGMENTARY AND PILOSEBACEOUS NEVUS

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Acne vulgaris is one of the many cutaneous diseases which has commonly been noted to flare up in Naval and Marine Corps personnel on duty in the tropics. This has been true aboard ship and at well established bases as well as under field conditions. The constant heat and increased humidity resulting in flushing and congestion of the skin and increased perspiration apparently favor its development. Changes in diet, neglect or inability to keep skin and clothing clean, emotional disturbances and many other factors are also doubtless important in individual cases.

Most important of all, however, in the causation of acne vulgaris is the inherent character of an individual's skin, especially as concerns the pilosebaceous apparatus. This is illustrated by the present case.

REPORT OF A CASE

A third class petty officer in the U. S. Naval Reserve, aged 18, was returned to the United States after approximately four months at an advanced base in the Southwest Pacific. As an incidental finding on arrival here it was noted that he had a localized eruption on the right side of the chest. The patient had been aware of a light brown pigmentation from his earliest childhood but no other eruption had been noted in this area, nor had he had acne vulgaris previously. The new lesions had appeared shortly after arrival in the tropics.

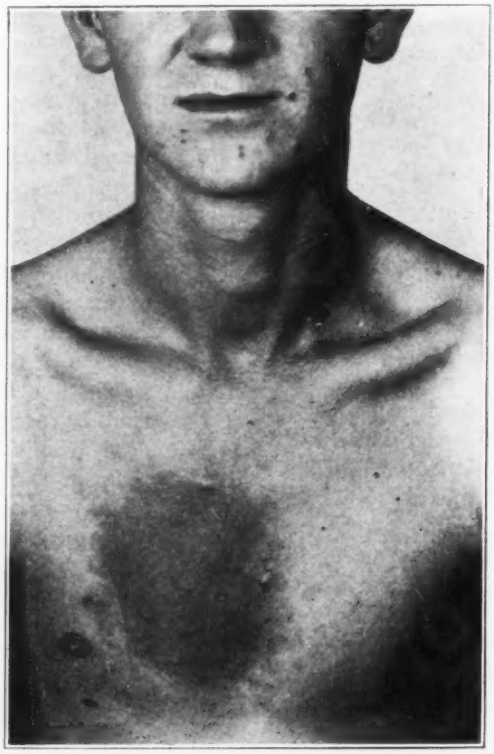

Fig. 1.—The lesions on the left side of the chin are pigmented nevi.

The eruption consisted of comedos and a typical papular and papulopustular acne vulgaris occurring in a nevus characterized by increased pigmentation and hypertrophy of the pilosebaceous apparatus. There were no acne lesions elsewhere except a few comedos and small papular lesions on the chin. The eruption promptly improved following his return to this country, leaving only the original nevus.

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EFFECT OF ENDOCRINE SUBSTANCES ON THE ADULT HUMAN SCALP

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AND
SAMUEL J. ZAKON, M.D.
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In a previous communication [1] we presented evidence to show that injections of testosterone propionate given over a short period produce an increase in the number and the size of the sebaceous glands of the pubertal region in boys of prepubertal age. This report deals with the effect of testosterone and diethylstilbestrol on the scalps of adult males.

METHOD

Two men were selected for this study. Subject A was 18 years old, with beginning premature alopecia, having lost about 20 per cent of his scalp hair during the previous year. He was under our observation for seven consecutive months and received the following treatment: (*a*) 40 mg. of methyl testosterone daily by mouth for the first three months; (*b*) no treatment during the month that followed, and (*c*) 5 mg. of diethylstilbestrol daily by mouth for the last three months.

Subject B was 34 years old and had a malignant alopecia areata for the past three years. About 90 per cent of the scalp was completely bald, eyelids and extremities were entirely devoid of hair and eyebrows, face, upper lip, chin and chest contained a few scattered hairs; the pubic hair was scant, but axillary hair was almost normal in amount. Physical examination and metabolism tests revealed nothing significant. He was under our observation for five consecutive months receiving (*a*) 40 mg. of methyl testosterone daily by mouth and 25 mg. of testosterone propionate twice a week intramuscularly for four months and (*b*) 5 mg. of diethylstilbestrol daily by mouth during the month that followed.

In both patients small portions from the occipital region of the scalp were removed for histologic study with the use of a biopsy punch before treatment and at the end of each treatment period.

From the Department of Endocrinology, service of Dr. H. Isaacs, and the Department of Dermatology, service of Dr. S. J. Zakon, Mount Sinai Hospital.

The androgen preparations used in this study were supplied through the courtesy of Roche-Organon, Inc., Nutley, N. J.

1. Rony, H. R., and Zakon, S. J.: Effect of Androgen on the Sebaceous Glands of the Human Skin, Arch. Dermat. & Syph. **48**:601 (Dec.) 1943

RESULTS

In subject A, increase in the amount of body hair was apparent during the period of testosterone therapy, and the scalp hair, which was dry, became noticeably oily. He believed that he lost less scalp hair during this period than before, but we could observe no noticeable regrowth of scalp hair. Histologic sections show decided increase in the number and size of the sebaceous glands in the scalp during this period (figs. 1 and 2), which change was not wholly maintained a month after use of testosterone was discontinued (fig. 3). During the period of administration of diethylstilbestrol, the mammary glands in the breasts responded with enlargement and with hyperpigmentation and hypersensitiveness of the nipples. On inspection no effects were noticed on the growth of scalp hair, and in the histologic sections the sebaceous glands were seen to have reverted to their original appearance (fig. 4).

Subject B reported itching of the scalp during the period of testosterone therapy. Some new lanugo hairs appeared on the spots that showed hair before treatment and also on some portions of the scalp that were previously completely bald; however, the total effect was practically negligible. The preliminary histologic sections show large sebaceous glands characteristic of alopecia areata (fig. 5), and there was further hyperplasia at the end of the period of administration of testosterone (fig. 6). During the period of therapy with diethylstilbestrol, there was a decided loss of scalp hair and other hair, and the patient refused to continue longer to take that estrogen. Histologic sections indicate definite atrophic effect on the sebaceous glands after ingestion of diethylstilbestrol.

COMMENT

Our finding that androgen has a stimulating effect on the sebaceous glands of the scalp in

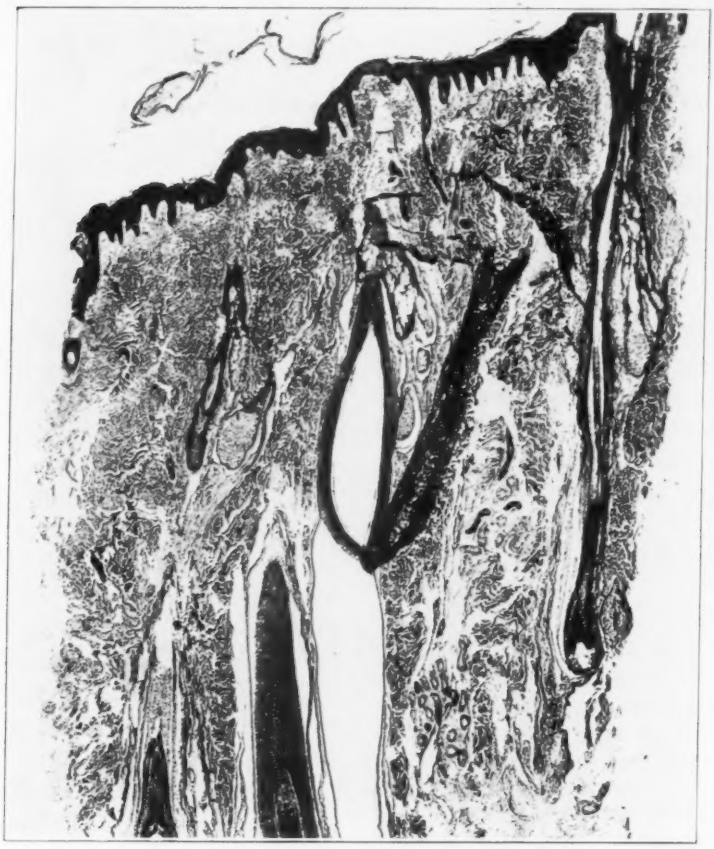


Fig. 1.—Section preliminary to treatment.

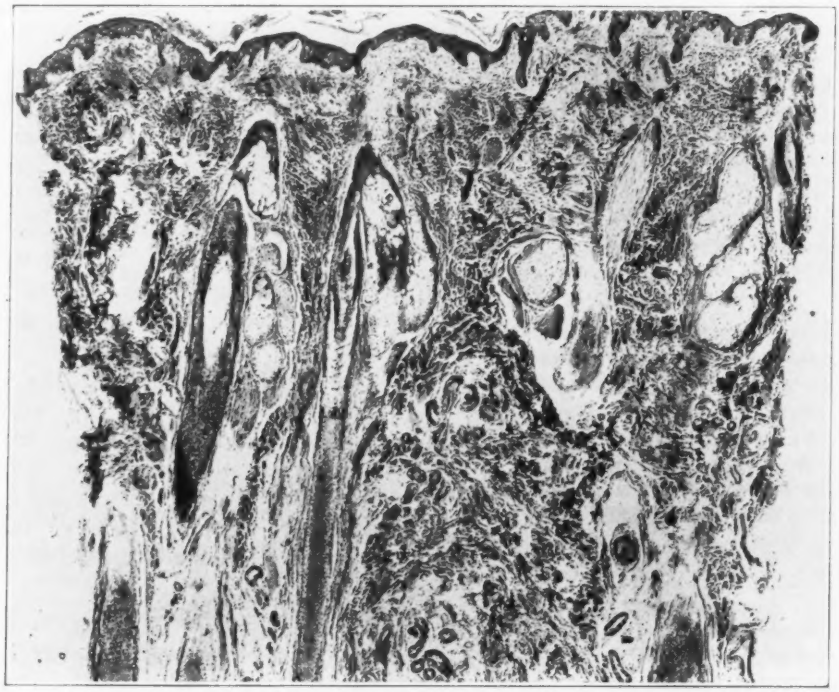


Fig. 2.—Increase in the number and in the size of the sebaceous glands after methyltestosterone therapy.

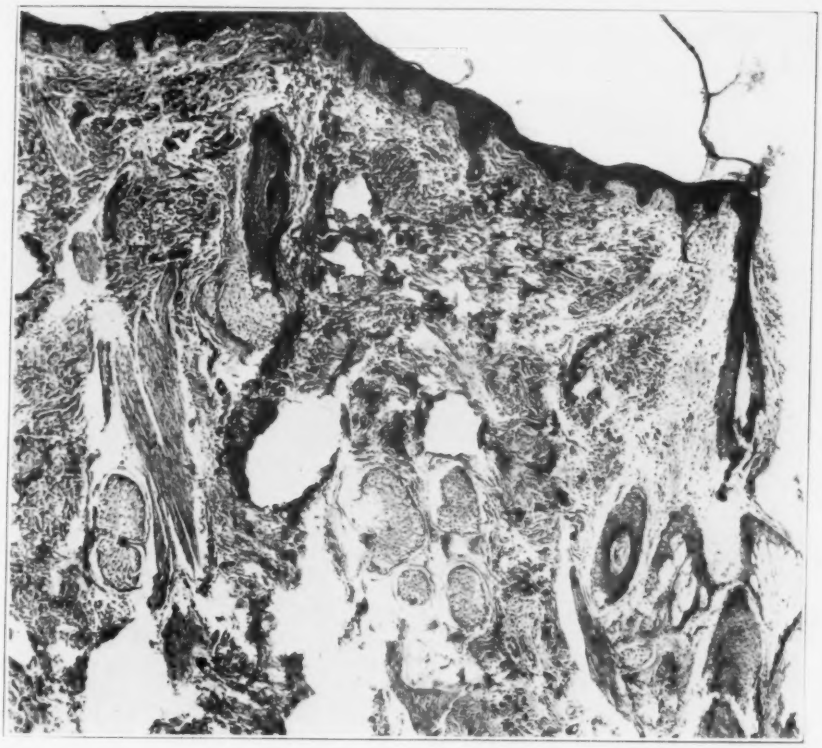


Fig. 3.—Decrease in the size of the sebaceous glands one month after methyltestosterone therapy was discontinued.

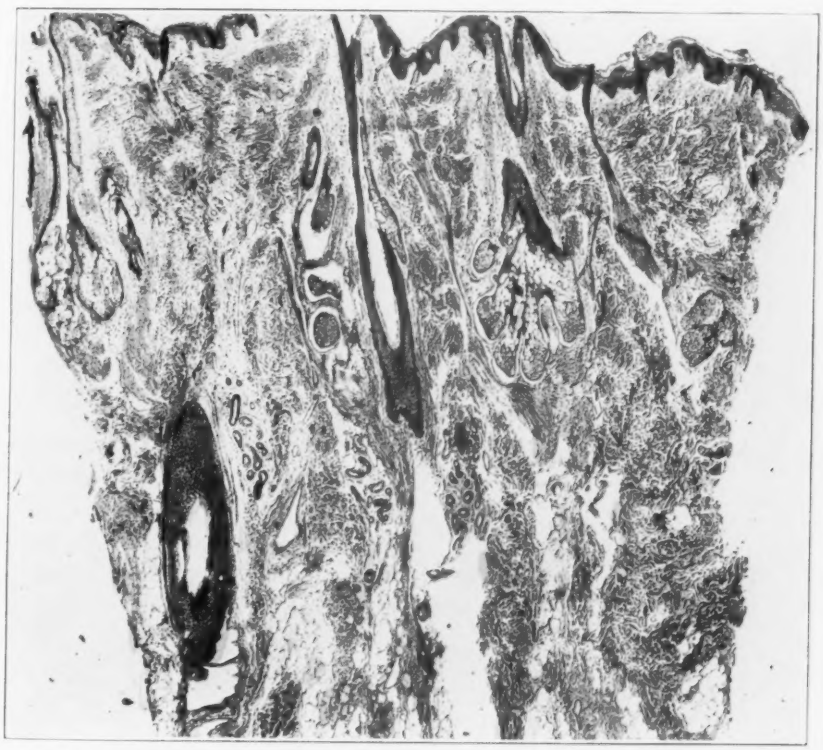


Fig. 4.—Reversion of hypertropic sebaceous glands to original state after diethylstilbestrol therapy. Compare with figure 1.

these adults (as well as on those of the pubertal region in prepubertal boys) indicates that stimulation of the sebaceous glands is a general effect of androgen, regardless of the location of these glands or the age of the subject. It is of interest to note that this effect is powerful enough to produce further growth of the already hyperplastic sebaceous glands of alopecia areata.

Our further finding that diethylstilbestrol causes reduction in size and number of the sebaceous glands in the human scalp is in agreement with Hooker and Pfeiffer's report [2] that the sebaceous glands of estrogen-treated rats become much reduced in size.

Attention is called to our observation that in the case of premature alopecia, testosterone, while stimulating the sebaceous glands in the scalp and the growth of body hair, did not promote the growth of scalp hair. This seems to indicate that the responses provoked by androgen in the hair follicles and in the sebaceous glands are two distinct and different phenomena: the one phenomenon depends on factors of regional character, inherent in the responding tissue; the other phenomenon seems to be independent of such factors.

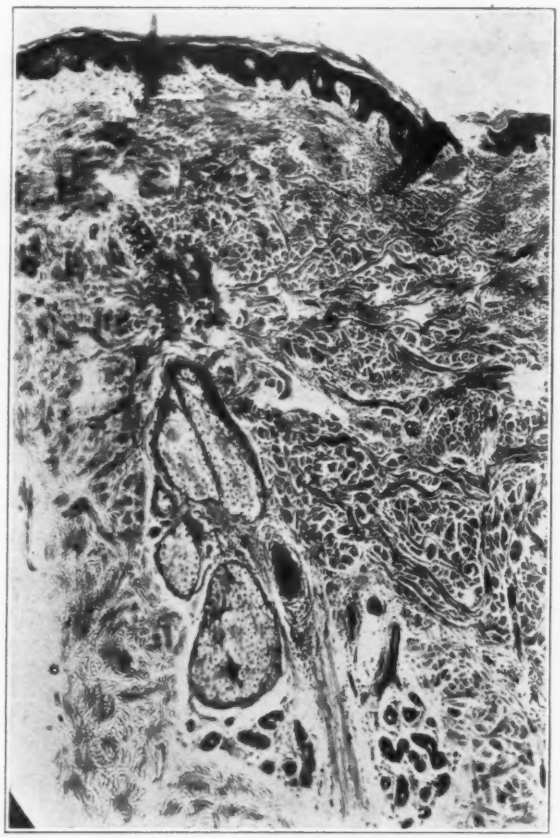


Fig. 5.—Section of alopecia areata prior to any therapy.

CONCLUSIONS

The androgen methyl testosterone has a definite stimulating effect on the sebaceous glands of the adult male as well as of the male of prepubertal age. The estrogen diethylstilbestrol has a depressing effect on the sebaceous glands of the adult male.

6 North Michigan Avenue.
1 North Pulaski Road.

2. Hooker, C. W., and Pfeiffer, C. A.: Effect of Sex Hormones upon Body Growth, Skin, Hair and Sebaceous Glands in the Rat, Endocrinology **32**:69 (Jan.) 1943.

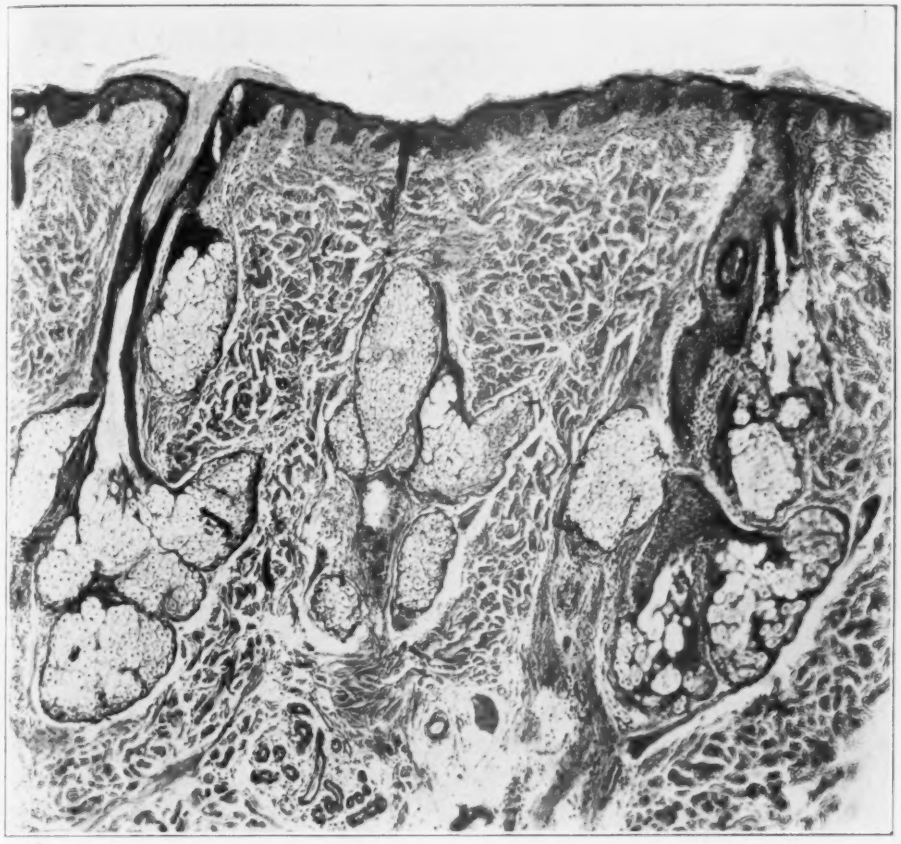


Fig. 6.—Decided hyperplasia of the sebaceous glands after methyltestosterone therapy.

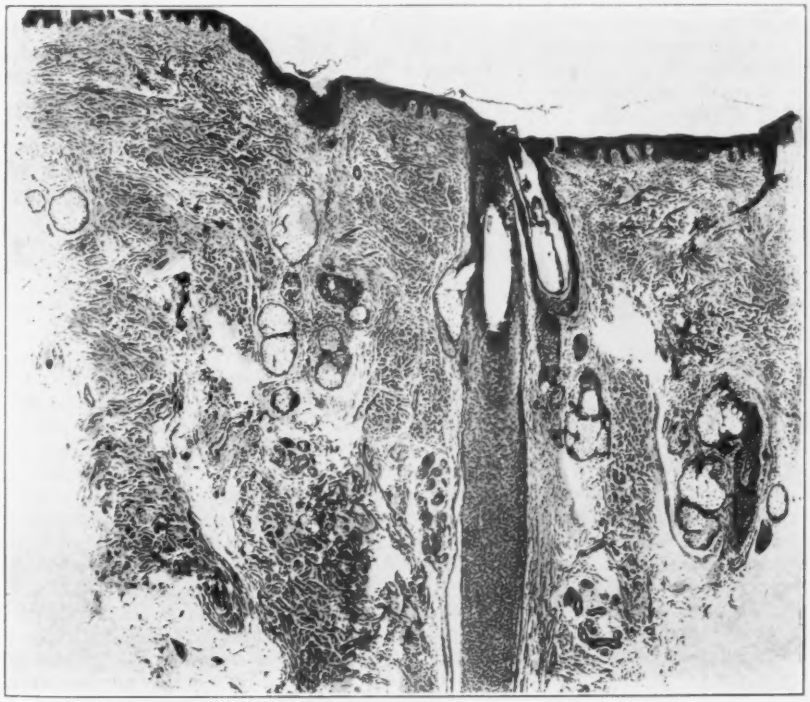


Fig. 7.—Pronounced atrophy of the sebaceous glands after diethylstilbestrol therapy.

EPIDERMODYSPLASIA HYSTRICOIDIS BULLOSA

REPORT OF A CASE WITH HISTOPATHOLOGIC STUDY

JOSÉ G. REYES, M.D.
NEW YORK

Under the name of epidermodysplasia hystricoidis bullosa a rare form of a congenital ectodermal malformation is here reported. The patient has been under my observation for more than one year, during which time a thorough study of the clinical symptoms and the histologic features of his disease has led me to the belief, after an exhaustive study of the literature on the subject, that this is so rare a disease that it has never before been reported.

REPORT OF CASE

The patient is an 18 year old native-born Puerto Rican, who came to this country two years ago. He weighs 91½ pounds (41.5 Kg.) and is 5 feet 3 inches (160 cm.) tall. While he is not mentally deficient, he is slow to grasp ideas; his behavior is normal, and he is conscious of his eruption.

Family and Personal History.—The mother claims to be well and in good health. She states that her husband died suddenly in 1938, of unknown cause. So far as she knows, no disease of the skin has been present in the family on either side, the boy being the only member of the family with such an ailment. She has had ten children, of whom three have died, and she states that all the children with the exception of J. R. (the patient), who was the eighth child, were normal in every respect. Of those living six are male and one female.

During the period of gestation with J. R. she felt a "kind of itch inside the womb" from the third month on, and, in order to obtain relief, she pressed and kneaded her abdominal wall. In addition to this unusual symptom she suffered from "morning sickness," which condition was also present during her other pregnancies; however, the "itch inside the womb" was present only during the pregnancy with J. R. The mother also relates that during this time she noticed a craving for hot peppers with practically every kind of food she took and that the onset of this longing was from the very beginning of the gestatory period. This yearning was not experienced during any of the other pregnancies.

At full term and after an uneventful period of gestation the child was born. The mother was in labor for five days, had excruciating pains and discharged large amounts of amniotic fluid. When the child was born, the mother noticed that he was entirely covered with a "starch-glue-like substance" which would not come off when washed with soap and water. She related that during his first three years of life J. R. was constantly having trouble with his skin in the form of "blisters," which broke open easily, leaving an exposed and raw surface. After the third year he improved, with only small areas being affected, the process beginning, as usual, with the formation of "blisters."

At birth the hair of the scalp was a solid mass of interwoven hairs and crusts; the projecting ends had to be cut off with heavy scissors, owing to their bark-like hardness. However, there was an area of baldness on the anterior part of the scalp. When the boy was 1 the hair began to improve in growth, consistency and distribution, and now that he is 18 the hair is normal as is also the hair of the eyebrows, the eyelashes, the pubic area and the dorsal surfaces of the proximal phalanges of the hands and feet, where it is found in scantier quantity than is usual in boys of his age. A slight down is now beginning to appear on the upper lip.

Symptoms.—The patient has a congenital patch of partial alopecia on the scalp, situated at about the left frontoparietal suture. It is half the size of a palm and is irregularly shaped, and its dry surface is covered with ichthyotic elements in the form of variously sized plaques. A few hairs, normal in every respect, are scattered on this patch. I believe that there must be a constant pruritic factor in this lesion, because every time I have examined it fresh scratch marks have been found, although the patient has never complained of pruritus. This area of alopecia is usually not visible because he combs his hair back, thus covering it. However, when the hair is streaming down over his face, it is noticeable.

The remaining part of the scalp seems to be normal except for the presence of fine furfuraceous slight greasy white and gray scales in abundance.

The face used to be covered with crusts of various sizes and forms, but when the patient was 3 years old it began to clear. Now the skin of the face and ears looks dry and is covered with small flaky scales, similar to those following ultraviolet irradiation but without the erythema. The face is free from crusts, but the ears are covered with a few pea-sized flat crusts. The color of the skin of the face and the ears is dark, typical of the people of his race.

His physiognomy is somewhat peculiar, although there is no prominent frontal bulge and no depression at the base of the nose.

The teeth are irregular in shape. The upper incisors are normally set, while the lower ones are widely separated, especially the middle ones, which form a V-shaped gap with the angle pointing toward the gum. The other teeth approach the conical type.

The mucous membrane of the mouth, tongue, lips, palate and nose is normal and free from any lesion. The same can be said of the conjunctivas.

The skin as a whole is dry, dark and harsh, and it is covered with scales and horny hypertrophic elevations which vary in size, shape and thickness. The skin around the elbows and knees is extremely thick and looks like the bark of a tree.

In general the lesions are multiform, but there are four predominating types: (1) slightly elevated quadrilateral plaques, somewhat darker than the neighboring skin, with rounded margins which gradually merge with the neighboring skin, located on the upper part of the

dorsa of both hands, the wrists, the lower third of the extensor surfaces of the forearms and both thighs, the largest of the lesions being about 1 cm. in diameter; (2) dark greenish elevated (about 2 mm.) cuboidal lesions, with perpendicular sides and a smooth top surface, located in the intermammary region and separated from each other by deep furrows; (3) slightly dark elevated (about 2 mm.) polygonal or round verrucous lesions, located in both inguinal regions and separated from each other by deep furrows, and (4) bullae, which are usually tense and contain a clear fluid, that are produced by external injury.

These lesions have the following distribution: The skin of the neck is dry and wrinkled; its normal lines are exaggerated and, in some areas, are covered with slightly raised grayish black crusts, producing rectangular and quadrilateral lesions, similar to those of lichen simplex chronicus of Vidal.

The lesions found in the supraclavicular areas are slightly more raised than those in the infraclavicular areas. The left clavicle is bulky and bulges forward, particularly at its junction with the sternum. The right clavicle seems to be normal.

The shoulders, axillas, axillary folds, upper extremities, chest, back, abdomen, flanks, inguinal areas and lower extremities are covered with variously sized and shaped lesions (oval, round or polygonal, cuboidal and quadrilateral), which are elevated from 1 to 3 mm.

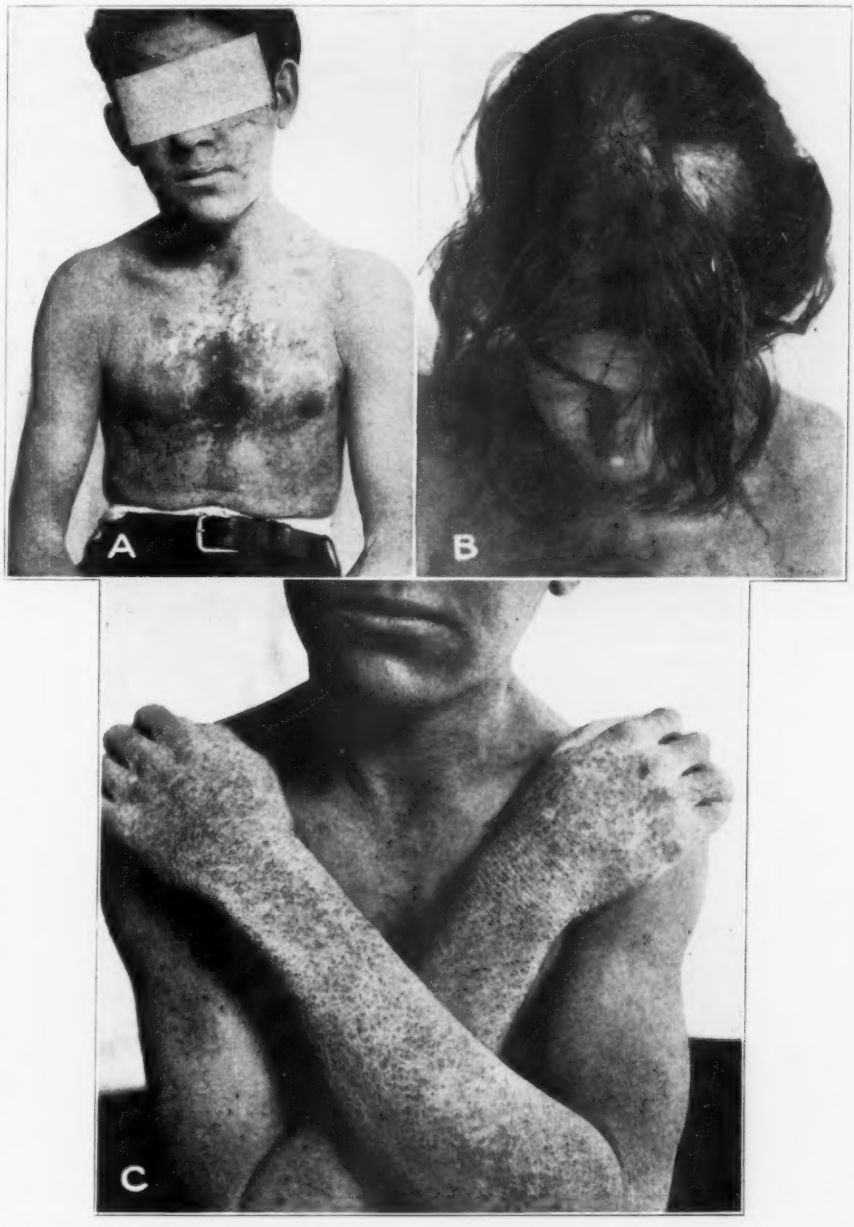


Fig. 1.—*A*, cuboidal lesions (darker part) of the hystrix type, on the chest; *B*, patch of congenital partial alopecia; *C*, plaques and the ichthyosiform features. (Note the ruptured bulla on the dorsum of the right hand at the third metacarpophalangeal articulation.)

above the *niveau*. Both the flexor and the extensor surfaces of the extremities are involved, as well as the cubital and popliteal flexures.

The lesions are closely set around the nipples and in the intermammary and pectoral areas. Those on the back are closely packed, especially on the upper part and along the line formed by the spinous processes of the vertebral column. The lesions on the nipples and around them, when closely viewed, give to the nipples the appearance of artichokes; they are almost black, especially at the very tips, and the central lesions attain an elevation of about 3 mm. The lesions of the intermammary area are cuboidal, flat topped and gray-green; they are separated by furrows and are raised about 2 mm., giving the appearance of gray-green stale dough cracked open by drying. The lesions below the pectoral areas and on the flanks follow the lines of cleavage of the skin and are small, verrucous and crusted, forming broken ridges running transversely to the axis of the body. The lesions on the abdomen are of the same type. Those on the lower part of the abdomen and in both inguinal areas take the form of thick broken lines, separated by furrows which follow the lines of cleavage of the skin. Those in the inguinal areas are of the polygonal or round verrucous type, raised about 2 mm. above the surface of the skin, and are of a dirty gray color. Some crusts of the flat type are noticed on the scrotum, the penis and the prepuce.

The area where the belt produces friction is more or less free of lesions. The sacroiliac and sacral regions are almost free of lesions of any type, and here the skin looks normal, a few healthy hairs being scattered throughout these areas. The normal creasings of the natal folds are exaggerated in the form of slightly raised ridges, which have a semicircular arrangement.

On the arms the lesions are oval, round or quadrilateral plaques, the last being the most predominant type, and are more numerous on the posteromesial aspects. These lesions are raised about 1 mm. from the surface of the skin, and the largest are found around the elbows, where they produce tremendous thickening and wrinkling.

On the forearms there are flat raised plaques, covering both the extensor and the flexor surfaces. The lesions on the extensor surfaces are larger and thicker and are elevated about 2 mm., while those on the flexor surfaces are raised only about 1 mm. The predominant lesions on the lower third of the forearms are of the quadrilateral type, which lesions are also found, but more pronounced, on the dorsal aspects of both wrists and the upper half of the dorsa of both hands. The lesions on the lower half of the dorsa of both hands and the dorsal aspects of the fingers are larger but less raised than those on the wrists. The skin of the dorsal surfaces of the terminal phalanges is thick and is covered with few crusts. The finger nails and the palms are normal.

The extensor, flexor, medial and lateral aspects of the lower extremities are covered with flat lesions of various sizes. However, those on the extensor surfaces are larger and more pronounced than those found on the backs of the thighs. The lesions of the popliteal areas appear in the form of broken elevated ridges following the normal creases of the skin and are similar in form to those found on the lower part of the abdomen and in the natal and axillary folds. The creases around the knees, especially in the patellar areas, are grotesque and largely exaggerated, and this skin when grasped between the fingers gives a barklike sensation to the touch. The muscles of the lower third of the right thigh are more highly developed than the corresponding ones on the other thigh, probably because of the patient's slightly irregular gait.

The lesions on the legs are flat, squamous and exfoliating and lie almost even with the skin; however, the lesions on the gastrocnemial areas are larger and more raised. Normal hairs are found here and there on the thighs and legs.

The lesions around the ankles are also flat; the skin is thickened, and its normal creasings are exaggerated.

The lesions on the dorsa of both feet are flat and squamous and are separated by fine furrows. The skin on the dorsal aspects of the toes is normal save for an occasional exfoliating scale here and there. The soles and toe nails are normal.

Since birth the patient has had vesicles and bullae appear on any portion of the body subjected to trauma, friction or injury. The same still is true now that he is 18. These bullae are tense and contain a clear fluid, which microscopically showed leukocytes and degenerated prickle cells. They rupture easily, leaving a smooth pink surface, which later becomes pigmented and finally becomes verrucous or ichthyotic. Some bullae, however, become secondarily infected; this complication is troublesome and demands attention, because the infection may easily spread to the neighboring areas. Thus, recently, the patient came to my office with a bullous lesion the size of a grape. It was located on the dorsal aspect of the second metacarpophalangeal articulation of the left hand and had been produced by a glancing blow. Its fluid was clear. Two days later the lesion ruptured, showing a pinkish and smooth area which looked dry. The exposed areas are extremely sensitive, especially when they come in contact with water.

None of the mucous membranes have ever been affected by either vesicles or bullae.

Despite the presence of bullae, milia—either grouped or solitary—are typically absent.

The patient has an odor which at close range is offensive.

I have seen the patient perspire freely during the summer months, thus indicating that his sweat glands are normal and active.

Histologic Study.—A specimen for biopsy was sent to Dr. Fred D. Weidman, University of Pennsylvania, who submitted a detailed report from his histologic study, a summary of which is given here:

There was an extraordinarily thick layer of hyperkeratotic material (psoriasiform) overlying the surface of the skin except for one region in the center; here the changes were such as to indicate the presence of excoriation. The keratinous substance was arranged in irregular lamellas, but, unlike those of psoriasis, they were extremely wavy and not sharply demarcated. Their wavy contour corresponded more or less to that of the epidermis underneath. It was clear that the surface of the epidermis was thrown up in low verrucous projections.

The stratum granulosum was also excessively thickened; in places it constituted fully half of the epidermis. It was vacuolated to such a degree that it could take on a reticulated pattern, with the cytoplasm of the cells disposed on a general region of edema which was traversed by strandlike remnants of the cytoplasm. In short, the picture was that of spongiosis but translated and largely confined to the uppermost regions of the epidermis. This spongiosis continued in places into the prickle cell layer but not into the stratum germinativum. Keratohyaline granules were abundant.

Fig. 2.—Low power view illustrating the extreme grade of hyperkeratosis and the degree of epidermal change underneath it by contrast with normal epidermis at either end of the section. Note that the thickening of the skin is accounted for mostly by changes in the upper parts of the epidermis.

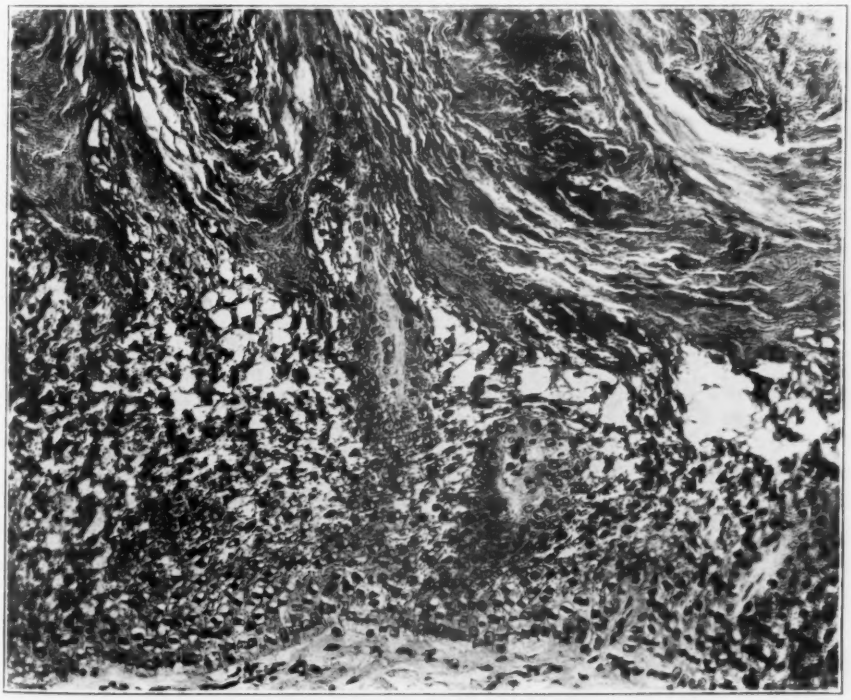


Fig. 3.—High power view showing a portion of the epidermis. In addition to the hyperkeratosis at the top of the photomicrograph, the details of epidermal change are demonstrated. The stratum granulosum is predominantly affected, thickened, increased in granule content and vacuolated.

The interpapillary pegs varied in length and shape but in general were not greatly elongated by any means or notably deformed. If anything, the epidermis was thin as regards the more viable parts in the stratum germinativum and spinosum. This fact indicates that the process was not fundamentally hyperplastic; the thickness of the epidermis was the result of abnormalities in the stratum granulosum together with their consequent product, keratin. In short, it was an abnormality of keratinization.

In the corium there were no important changes. The papillae were normal except for deformity consequent on whatever irregularity there was in the interpapillary pegs. Around the blood vessels there was but a minor grade of edema and lymphocytic infiltration.

The pilosebaceous apparatus and sweat glands were numerous, highly developed and apparently normal. Perhaps the sebaceous glands were hypertrophic, and the same may have been true for the sweat glands. This statement cannot be made positively without a study of control specimens from normal ipsilateral positions.

As confirmed by sections stained by Weigert's method, elastic tissue was entirely absent in the uppermost parts of the skin. Farther down it was present in small quantities, and such as there was was grouped into local aggregations and was highly fragmented.

In summarizing and interpreting Dr. Weidman's observations it becomes apparent that the scarcity of elastic tissue was consistent with epidermolysis bullosa. The fact that pathologic changes were almost entirely in the stratum granulosum and stratum corneum was consistent, too, with ichthyosis. The thickness of both of these layers was striking, as was the form which the changes in the stratum granulosum had taken.

Laboratory Observations.—The chemical examination of the blood showed: blood sugar 83.3 mg. per hundred cubic centimeters, urea nitrogen 16.9 mg., nonprotein nitrogen 35.15 mg., uric acid 2.3 mg., cholesterol 120 mg. and calcium 10 mg.

The urine was yellow and clear, with no sediment and was acid in reaction, with urinous odor. The specific gravity was 1.026, and total solids measured 5.7 per cent. There was no blood, albumin, diacetic acid, bile, dextrose or acetone detectable in the urine. The indican content was normal. The urea content measured 1.8 per cent of the volume. The microscopic examination did not show mucous threads, pus cells, epithelial cells, red blood cells, cylindroids, casts, phosphates, uric acid or calcium oxalate. Only a few amorphous urates were found.

The basal metabolic rate was subnormal; the Wassermann reaction of the blood was negative.

GENERAL CONSIDERATIONS

Differential Diagnosis. — Epidermodysplasia hystricoidis bullosa has to be differentiated from other diseases due to anomalous formation of the ectoderm.

1. Ichthyosis, which, according to Darier,[1] "is never congenital but which manifests itself at an early age," must be ruled out. In my patient the disease is congenital. In a patient with ichthyosis the palms and soles are usually dry and wrinkled, while in my patient they are normal. In ichthyosis the cubital flexures, the popliteal areas, the groins, the articular and axillary folds and the genitalia are almost normal, while in epidermodysplasia hystricoidis bullosa all these areas are covered with lesions of various types. In ichthyosis the sweat and sebaceous secretions are notably diminished in contradistinction to the increases observed in my case. Ichthyosis is usually aggravated by cold weather, but my patient's disease has improved during the winter months. In ichthyosis the hair becomes dry and the nails brittle, breaking easily; this is in contrast to the condition seen in my case.

2. In patients with epidermolysis bullosa one finds single or grouped milia, which are entirely absent in my patient. In cases of epidermolysis bullosa the bullae are sometimes hemorrhagic, while in my case this has never been observed. In epidermolysis bullosa, the nails may show dystrophic changes and the mucous membranes of the mouth and tongue may be affected with bullae or patches of leukoplakia, while in epidermodysplasia hystricoidis bullosa they are normal. In patients with epidermolysis bullosa the healing of the bullae may be followed by scarring, but this has never been noticed in my patient, and, last, patients with epidermolysis bullosa reveal a significant hereditary or familial history, which my patient does not have.

3. In patients with pachyonychia congenita of Jadassohn [2] the nails are thickened, folded longitudinally, opaque and lusterless. There are also palmar and plantar hyperkeratoses, anomalies of the hair and leukoplakia. Verrucous lesions occur on the elbows, knees, popliteal regions, buttocks, leg and ankles, with bullae occurring chiefly on the plantar surfaces. In my patient, the nails, palms and soles are normal; there is no leukoplakia, and the partial alopecia in the scalp is outstanding.

4. In cases of erythroderma ichthyosiforme congenitum there is a generalized erythroderma, which later in the patient's life may disappear, leaving an ichthyotic skin; the picture of the disease is that of ichthyosis plus redness. Unlike the distribution in my case, the flexor surfaces are the sites of predilection for this disease. The palms and soles, the buccal and nasal mucosas and the eyes are invaded to a variable degree, and the face is usually red. The bullae occur as a complication, appearing most fre-

1. Darier, J.: Precis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, p. 254.

2. Cited by Sutton, R. L.; and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 561.

quently on the extremities, and are of the flaccid type, disappearing without sequelae to reappear during the winter months. As a rule they disappear permanently when adult life is reached. Perspiration is limited except on the flexures of the extremities and on the palms and soles. In my case, again, there is a patch of partial alopecia in the scalp.

The histologic features of epidermodysplasia hystricoidis bullosa might suggest several other conditions in which it is known that the fundamental pathologic changes are those of an epidermodysplasia. All these, however, can be eliminated on clinical grounds, particularly because they are not ichthyosiform. Mention is made in this connection of only a few.

5. In nummular and confluent papillomatosis the lesions are verrucous nummular papules, with reddish reticulum. In 1 case the onset occurred when the patient was 13 years old, the intermammary area being affected first. The scalp was normal.

6. In verrucous papillomatosis (Gougerot, Clara and Bonnin [3]) the lesions are round raised brownish papules, elevated about 1 to 2 mm. The area first affected is the dorsa of the hands, then the wrists and the forearms and, later, such areas as the face, neck and palms. The volar surfaces and the scalp are not affected at all, and the onset is in adult life.

7. In epidermodysplasia verruciformis (Lutz and Lewandowsky [3]) the lesions are found all over the body in the form of plates, 1 to 2 cm. in diameter, and pale red or reddish papules, which may be round, oval or polygonal, with straight margins, even surfaces and no trace of pigmentation. Grayish scales are also noted, which may be removed. The scalp is involved from early life. The lesions in this disease are present at birth.

8. In punctate papillomatosis (Gougerot and Clara [3]), the lesions are punctate verrucous papules, which affect the neck, the trunk and the extremities. There is also stippled erythema of the face and scalp and porokeratosis of the palms and soles. The onset of the disease in the case reported [3] occurred when the patient was 13 and the lateral parts of the body were affected, from whence it spread to other areas. The eruption disappeared during the months of autumn and winter. The seborrheic regions of the body were especially involved. On the scalp and on the face there were crusts which when removed exposed small ulcers.

9. In confluent and reticulated papillomatosis the onset occurs between the fifteenth and twenty-sixth years of life. The lesions first appear in the intermammary area, where they take the form of verrucous papules, varying in size from 1 to 2 mm. in diameter, and are a deep gray. As a rule, confluence occurs in such a way that reticulated areas are formed. The scalp remains normal.

Prognosis.—The prognosis as to life is good but as to cure is a moot point.

Treatment.—At present nothing definite can be said regarding treatment, inasmuch as no good results have been obtained from the external and internal medications used. Singularly, the patient states that he has been greatly benefited by the change of climate brought about when he came to New York from the tropics.

COMMENT

In substance, the changes previously described indicate that the pathologic processes are of two kinds. First, there is hyperkeratosis, both clinically and histologically evident. Microscopically, it takes the form that justifies the designation "epidermodysplasia"; this is consistent, incidentally, with the characteristics exhibited in ichthyosis as well as in other entities. There is a circumstance additional to the picture typical of ichthyosis in that there is a patch of incomplete alopecia in the scalp; since it was congenital, it must be regarded as a part of the original pathologic processes and not secondary thereto. This being the case, it appears logical to explain the loss of hair on the basis that the abnormal keratinization included the hair papillae as well as the surface epithelium and led to disappearance of hair. It is granted that this theory is speculative, and it is submitted in the absence of any reasoning that is more appealing. I have no explanation why the nails, palms and soles did not participate in the abnormalities of keratinization.

The second kind of change is of the order of that which occurs in epidermolysis bullosa—again, with respect both to clinical and to histologic phenomena (bullae, the traumatic factor and the scarcity of elastic tissue). In summary, in my patient there were two congenital shortcomings: one, concerning keratinization, and the other, concerning elastic tissue. Both of these shortcomings were demonstrated histologically, and thereafter the line of reasoning in relation to the clinical picture follows the conventional path of ichthyosis and epidermolysis bullosa.

3. Cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 870.

SUMMARY AND CONCLUSIONS

The name chosen for this disease conforms to the clinical and histologic observations. It is a congenital ectodermal abnormality with characteristics of its own. Clinically, there are a congenital patch of partial alopecia in the scalp, a congenital ichthyotic skin and the exuberant warty excrescences of ichthyosis hystrix and bullae, which are produced by external irritation or trauma through a congenital factor and which heal without scarring. Histologically the disease is an epidermodysplasia, because the bulk of the pathologic changes are located in the upper layers of the skin; as in ichthyosis, the main pathologic features occur almost entirely in the stratum granulosum and the stratum corneum. Moreover, as in epidermolysis bullosa, there is a congenital loss of elastic tissue and, last, in connection with a congenital ichthyosiform dermatosis, certain additional features may appear, which cannot be reconciled with any of the existing dermatologic entities that are more or less ichthyosiform. The most important of these are (*a*) a patch of congenital partial alopecia of the scalp; (*b*) the absence of changes in the nails, mucous membranes, hair, palms and soles; (*c*) the occurrence of bullae in a congenital ichthyotic skin and (*d*) the absence of milia.

Accordingly, it appears to be proper to apply a special term for the condition; namely, epidermodysplasia hystricoidis bullosa.

NOTE:—After this paper was completed and was ready to be submitted, I encountered another case of epidermodysplasia hystricoidis bullosa at a local hospital. This patient was an American-born white youth of 18, whose disease was diagnosed as ichthyosis hystrix with vesiculations.

791 Prospect Avenue.

DERMATOLOGY IN AN ARMY STATION HOSPITAL SERVING IN ITALY

CAPTAIN EMORY LADANY
MEDICAL CORPS, ARMY OF THE UNITED STATES

The relative position and functions of the dermatologic section in any hospital are generally the same as in any other, whether it be a department of a civilian hospital, of an army hospital in the continental United States or of an army hospital on overseas duty. One can reasonably expect, however, some variations and differences in the problems and procedures of dermatologic practice in hospitals of different nature, organization and geographic location.

An army hospital serving overseas usually has some limitations of equipment, supplies and personnel which hospitals in the Zone of the Interior do not as a rule have. Sanitary conditions under which soldiers have to live at the front, in bivouac areas and in replacement centers behind the lines may account for a higher number of bacterial and parasitic diseases of the skin than may be seen in hospitals in the United States. Parasites peculiar to a geographic area may cause a higher incidence of a particular type of parasitic diseases. The number of such diseases may be increased by the poor sanitary conditions of the civilian population with which soldiers come in contact, such as the populations of the zones of military operations and of war-torn cities and villages.

Under combat conditions, not only is the soldier exposed to infections but also facilities for early treatment may be lacking, so that when treatment can be obtained after some delay an otherwise banal cutaneous disease may be so aggravated that the soldier has to be hospitalized for an extended period. For instance, in many cases of scabies, the most simple medication cannot be carried out because of rough combat conditions. Such delay may result in a more or less severe pyoderma and makes hospitalization necessary for a disease which is routinely treated by battalion medical officers when handled under better living conditions.

Chronic cutaneous diseases which in favorable circumstances do not cause any discomfort may be aggravated by exposure to cold, strenuous marches and poor sanitary conditions. The mildest forms of psoriasis may send soldiers to the hospital after some time on the front line. Soldiers with congenital ichthyosis who had never been hospitalized in civilian life or when stationed in the continental United States, may have to spend weeks in the hospital after the onset of cold weather, when exposure and lack of bathing increase their complaints. Soldiers in combat units, wearing woolen clothes all through the hot summer months and woolen underclothes in the winter, who previously were not accustomed to wearing wool for an extended period, may and often do get sensitive to wool, and acquire extensive contact dermatitis.

Under the stress and strain of war, neurodermatitis, both the disseminate and the lichen simplex chronicus (neurodermatitis conscripta) types, causes increased complaints and gets more attention from the patient's finger nails, securing him not only some pleasure and relief from emotional tensions but often an easy means to escape rough conditions and combat. On the other hand, owing to the general good health and the age of soldiers on overseas duty, some types of cutaneous disease are seen only rarely in hospitals serving front line troops, diseases which may be seen routinely by dermatologists practicing in civilian hospitals. Such dermatoses may be manifestations of the various allergies, contact dermatitis connected with civilian occupations, dermatoses affecting the younger and the aged groups or chronic and incapacitating diseases of the skin precluding military service.

Army dermatologic practice in a station hospital serving in Italy may show some differences from practice in other geographic areas, which may be of interest to dermatologists in civilian hospitals, army dermatologists in the Zone of the Interior or in other theaters of operations.

The hospital to which I have been assigned has been in operation on the Italian peninsula for over a year. Many station hospitals on overseas duty handle their dermatologic patients casually among the various medical admissions, owing to lack of trained personnel or to limited facilities. This hospital has a dermatologic section with facilities and personnel adequate to care for most types of dermatologic cases.

THE DERMATOLOGIC SECTION

The dermatologic section of an army hospital is a subdivision of the medical service. While in some hospitals the dermatologic department cares also for the patients with venereal disease and often include patients with syphilis, in this hospital the dermatologic section excludes persons with venereal disease. Patients with syphilis, penile lesions, gonorrhea and lymphogranuloma venereum are treated in the urologic section, which is in charge of a urologst.

The dermatologic department has a sixty bed ward and an active outpatient clinic, located in a permanent building sufficiently repaired and altered to secure comfort for the patients. Between the two wings of the ward, a spacious office was built to serve as the administrative office, examination and treatment room and also as the outpatient clinic. A smaller compartment attached to it serves as a storeroom for medicines and dressing materials and also as the place for routine ward treatments dispensed by the nurse or trained technician. The nurse's desk and the patients' waiting room occupy the remaining space between the two ward wings. A diet kitchen, a storeroom for linen and two wash closets, each with one sink, are parts of the ward proper. Water is heated on oil heaters or on a small electric plate, according to the amount required. Electric lights and facilities for heating are adequate. Bathtubs, showers and latrines are located in another building of the hospital. This is slightly inconvenient in the management of the occasional seriously ill bed patient. Recently a bathtub has been installed in the ward.

The equipment consists of the simplest instruments for examination and treatment. The beds are partly steel hospital beds and partly folding field cots. Furniture such as bedside tables, benches, examination tables and desks is homemade with the help of patients and Italian labor. Routine laboratory work is done in the laboratory of the hospital. Biopsy specimens are sent to a general army laboratory stationed nearby. Roentgenologic treatments, diathermy and short wave diathermy are not available, but the physical therapy section has a good air-cooled ultraviolet lamp, which is used largely for the treatment of patients with cutaneous disease.

The personnel consists of an officer dermatologist in charge, two nurses and a sergeant wardmaster, all of whom are trained and skilled in nursing patients with cutaneous ailments.

A skilled noncommissioned officer serving as clinical assistant is in charge of the clerical details and the outpatient clinic. One or two wardmen, more or less subject to change, and an Italian laborer make up the rest of the personnel.

While some morning hours are reserved for the outpatient clinic, the location of this clinic in the ward office makes it possible to see outpatients any hour of the day. Patients, who often come from great distances for consultations, do not make unnecessary trips on account of restricted hours. Suitable arrangements with the pharmacy and with the physical therapy section make it possible to see any patient, make a diagnosis, treat him and supply him with the necessary medicine, within a short time, so that he can return to duty without unnecessary loss of time. His return visits are kept at a minimum.

SOURCES OF ADMISSION

Patients are admitted from a number of units, such as base section troops, service units, replacement centers and training and reconditioning units stationed within a certain area around the hospital. Soldiers are seen at the daily sick call by the unit medical officer, and if this officer thinks hospitalization is necessary he forwards them to the admitting office of the hospital. Otherwise, a great percentage of patients with routine dermatologic diagnoses are treated by the unit medical officers and are sent to the outpatient clinic of the hospital only if diagnoses should be difficult or treatment is unsuccessful. Most patients with scabies seen at the outpatient clinic are treated while on duty; only those in whom extensive secondary lesions and pyodermas develop are admitted to the hospital. The treatment of psoriasis is also managed on the outpatient basis, unless the lesions incapacitate the soldier to the extent that he cannot keep up with his regular duties. Most patients with pityriasis rosea are not admitted, but they visit the physical therapy section for ultraviolet treatments on one to six occasions. After the diagnosis has been made and a soldier is supplied with the necessary medicines and instructions, he is usually returned from the outpatient clinic to the care of the unit medical officer. However, in some cases treatment cannot be carried out successfully under the conditions in which the soldier has to live, and the unit medical officer returns the patient to the hospital for admission.

Other sources of admissions are the evacuation hospitals stationed immediately behind the front lines and the overflowing station or general hospitals.

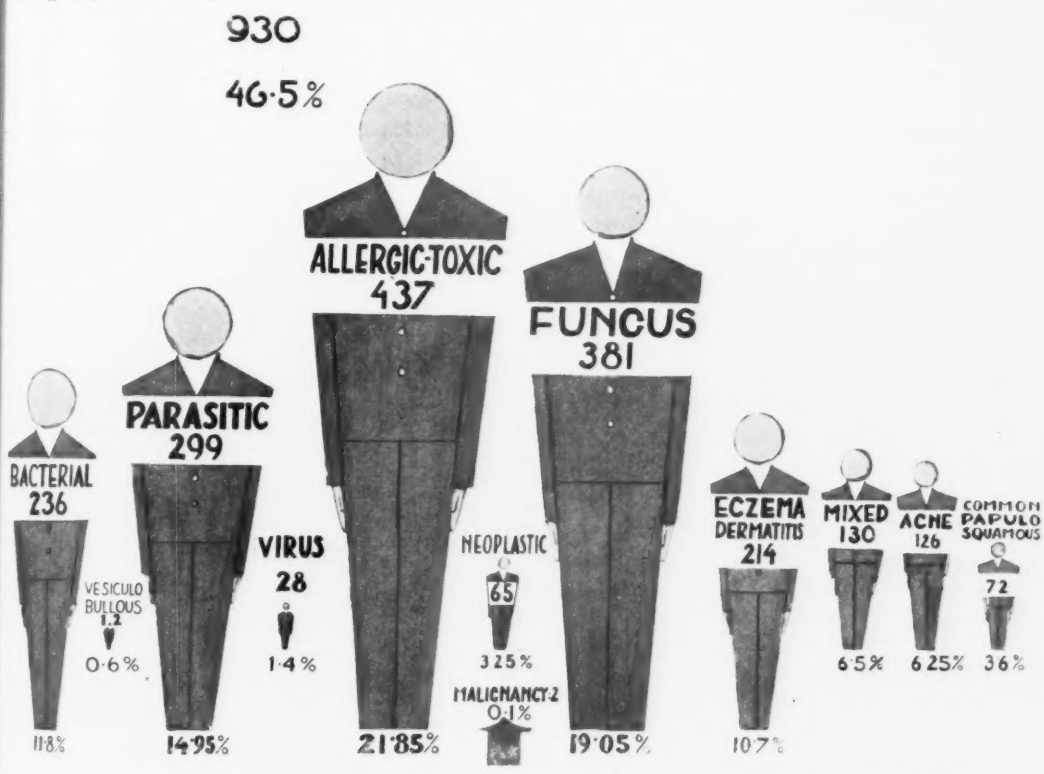
Patients primarily admitted to this hospital for other than cutaneous diseases and having a concurrent complaint of a cutaneous nature are also seen at the outpatient clinic unless they

are strictly confined to bed. If their cutaneous disease outweighs their other medical or surgical ailments, they are transferred to the dermatologic ward.

Patients without cutaneous diseases are admitted to the dermatologic ward only if shortage of bed space in other general medical wards makes such a temporary measure necessary.

STATISTICAL DATA

In the first year of operation of this hospital of all patients hospitalized, 5.3 per cent were admitted on account of cutaneous diseases, excluding syphilis and penile lesions. This number represents the percentage of patients treated for cutaneous conditions in the dermatologic ward. Some patients with furunculosis, ecthyma, cellulitis due to trichophytosis and other diseases were treated in the general medical or surgical wards and were not brought to the attention of the dermatologist. These are not included in the previously mentioned percentage. This is a considerably higher percentage than those published in reports from hospitals in the Zone of the Interior. Woolhandler[1] reported 2.6 per cent of patients hospitalized in the station hospital at Fort Belvoir, Va., for dermatologic disease. The reason for the higher percentage in this overseas hospital may be a high percentage of cutaneous infections under combat and field conditions, under which a majority of soldiers overseas live. It may also be due to the lack of facilities for early treatment and to the consequent aggravation of otherwise harmless acute or chronic cutaneous diseases. Lack of adequate quarters and of hot water make the application of hot compresses impossible for a soldier whose home is a tent or a bomb-damaged house, and, although he may not be seriously affected, he must be hospitalized in order to carry out comparatively simple home treatments.



Comparative sizes of the eleven diagnostic groups into which 2,000 dermatologic patients (930 [46.5 per cent] inpatients and 1,070 [53.5 per cent] outpatients) in an army station hospital in Italy were divided.

The yearly average hospital stay was nineteen and two tenths days. Patients were returned to duty as soon as their condition made it possible to carry them on ambulatory treatment by their unit medical officer, with occasional visits to the outpatient clinic of the hospital. One and three tenths per cent suffering from various chronic and partially disabling cutaneous diseases were boarded after improvement and discharged to limited service. Four and five tenths per cent of all patients suffered from cutaneous diseases necessitating a long period of hospitali-

1. Woolhandler, H. W.: Dermatology in an Army Station Hospital, Arch. Dermat. & Syph. **49**:91 (Feb.) 1944.

zation or causing serious disabilities and were transferred to general hospitals for further treatment or evacuation to the Zone of the Interior.

My colleagues and I have compiled statistical data on the first 2,000 dermatologic patients at this station hospital and analyzed and grouped them according to diagnoses. Of this number, 930 (46.5 per cent) were ward patients and 1,070 (53.5 per cent) were patients seen in the outpatient clinic. The ratio of hospitalized to clinic patients is also greatly at variance with the figure reported by Woolhandler.[1] He found in the Fort Belvoir Station Hospital that for each patient hospitalized there were 6.5 outpatients, whereas my ratio is 1 : 1.2. My ratio, therefore, is much closer to the figure reported by Pillsbury, Sulzberger and Livingood [2] from the Indiantown Gap Station Hospital, where the ratio of ward patients to outpatients was found to be 1 : 1.67. The number of average daily visits at the outpatient clinic of this hospital was 12, a figure corresponding closely to 14, that was reported by Woolhandler from the Fort Belvoir outpatient clinic.

We have analyzed the cases and placed our 2,000 patients in eleven diagnostic groups, using as a basis for this grouping the Pillsbury-Sulzberger Army "Manual of Dermatology."[2]

Our largest group, 437 patients (21.85 per cent), was comprised of the patients with allergic-toxic dermatoses. In this group we included all with allergic, contact and atopic cutaneous manifestations, urticaria, angioneurotic edema, dermatitis medicamentosa, dermatitis venenata, toxicoderma, erythroderma and erythema multiforme. The inclusion of persons with so many different entities may be the reason for this group's taking precedence over the next group, the patients with fungous infections, which in Woolhandler's report shows the highest percentage. Fungous infections were also the cause of the bulk of admissions for cutaneous diseases in hospitals of the Pacific theater, according to the communication of Ambler.[3] While it would be expected that one might see a large number of cases of dermatitis venenata caused by plants in most regions of overseas theaters, I have noted the rarity of such eruptions in our department. Woolhandler reported 68 cases of miliaria rubra among his 3,000 dermatologic cases. In our hospital, only a few cases of this disease were seen, undoubtedly not on account of its rarity in this region, but rat[her] because patients with this type of cutaneous di[s]ease were treated successfully at the battalion a[id] stations and were rarely seen at hospitals i[n] consultations or treatments.

Our second largest group, 381 patients (19[.]per cent), was that of patients with the fungo[us] diseases. We have noted the high incidence [of] fungous infections as secondary complications [of] the numerous cases of trench foot which ca[me] under my observation. Many patients in wh[om] trench foot developed in the rainy or cold seas[on] contracted trichophytosis pedis either before th[ey] were admitted to the hospital or soon after th[eir] discharge. Some with apparently improv[ed] trench foot were doing well until the hot su[m]mer months when, after even short marches, th[ey] came down with severe trichophytosis pedis, su[f]fering with continuous relapses thereafter ev[en] if they did not do extended marching or exerci[se]. Hyperhidrosis, bromhidrosis, excessive pustu[la]tion, cellulitis, spreading of infection along th[e] legs, contact dermatitis and resistance to trea[t]ment were other features of post-trench-fo[ot] trichophytosis. As relapses were common, i[n] manding frequent hospitalization, we were he[si]tant to discharge these patients to duty before [the] signs of infection were completely cleared. So[me] of them had to be evacuated to the Zone of th[e] Interior as unfit for general as well as for li[m]ited duty.

All fungous infections were of the superfic[ial] type, and we did not encounter any of the de[ep] fungous infections.

The parasitic diseases were represented [in] 299 patients (14.95 per cent), the majority [of] whom had scabies, so common in some parts [of] Italy. Our figure does not, however, show [the] actual incidence of parasitic infestations of ov[er]seas troops because of the fact that persons wi[th] uncomplicated infestations are treated routine[ly] by the battalion medical officer without ev[er] coming to the attention of the hospital derm[a]tologists. For the same reason we have se[en] only a few persons with pediculosis pubis, pedi[c]ulosis corporis and pediculosis capitis. Mo[st] tick bite lesions seen were fibrous nodes of lo[ng] duration contracted in most cases during maneu[v]vers in the Zone of the Interior, the chronici[ty] being due to manual irritation.

Patients with dermatoses due to bacterial [in]fections were found to number 236 (11.8 p[er] cent), the fourth largest group in our seri[es]. While most reports from Africa indicate a gr[eat] incidence of ecthymatous, chronic pyoderm[a] often called "desert sores," our impression w[as] that in Italy the majority of pyodermic lesio[ns]

2. Pillsbury, D. M.; Sulzberger, M. B., and Livingood, C. S.: Manual of Dermatology, Philadelphia, W. B. Saunders Company, 1942, p. x.

3. Ambler, J. V.: Experience of a Dermatologist in the Southern Pacific, Arch. Dermat. & Syph. **49**:224 (March) 1944.

were of the most superficial variety. A large number of these impetigo contagiosa infections could be traced back to native barbers. The extreme chronicity and discouraging resistance to treatment of many cases of impetigo and ecthyma were found to be due to the patient's persistent scratching. In the background of these pyodermas, one could discover as the primary factor exposure to insect bites, a low grade contact dermatitis, psychogenic pruritus or masked scabies and sometimes lack of cooperation and conscious malingering on the part of the patient.

Patients with infectious eczematoid dermatitis were also included in this group. We have not seen any definite tuberculous disease of the skin. One patient with lupus erythematosus and 1 with lichen nitidus came under my observation.

The fifth group, with 214 patients (10.7 per cent), was composed of persons with the eczematous eruptions not directly due to infection or allergy, such as the nummular eczemas, seborrheic dermatitis, neurodermatitis (both the disseminate and the lichen simplex chronicus varieties) and also all with secondary dermatitis.

The sixth, or mixed, group, with 130 patients (6.5 per cent), was comprised of persons with various and less common cutaneous diseases. In this group we included those with malformations, purpuras, metabolic dermatoses, anomalies of pigmentation and such entities as ichthyosis congenita, vitiligo, cutis verticis gyrata, neurofibromatosis (Recklinghausen), angiokeratoma (Mibelli), porokeratosis (Mibelli) and keratosis blennorrhagica.

In the seventh group, the group with acne, there were 126 persons (6.25 per cent), including those with all types of acne. They represent only the persons with the severe types of acne coming under our observation and do not include those in whom acne was incidentally found during treatment for other diseases. While in civilian life or under fair living conditions, acne may not be a handicap in a person's occupation it may incapacitate a soldier in combat to the extent that he has to be evacuated to a hospital for treatment. The majority of this number were treated at the outpatient clinic. All patients admitted to the hospital had severe and extensive acne, requiring elaborate care. In 2 instances the disease was so incapacitating that the patients had to be transferred to a general hospital for eventual evacuation to the Zone of the Interior.

The eighth group included all the patients with common papulosquamous dermatoses, numbering 72 (3.6 per cent). The majority of this group was made up of those with psoriasis of all types and severity, an occasional one with pityriasis rosea, patients with all types of lichen and patients with diseases of the parapsoriasis group, with diagnoses of pityriasis lichenoides chronica and pityriasis lichenoides et varioliformis acuta.

The ninth group, with 65 patients (3.25 per cent), included those with neoplastic lesions, benign and malignant. The bulk of this group consisted of persons with warts and nevi of all types. I have noted 2 patients with malignant growths in the 2,000 whose cases were analyzed. One of them was a soldier 28 years old, with a history of a previous operation for a new growth on the left side of his face and a present ulcerating squamous cell epithelioma lateral to the right eye. The other was a 32 year old soldier with a slowly developing node on the left side of his nose which was proved to be a basal cell epithelioma by histopathologic examination.

In the tenth, or virus, group, we had 28 patients (1.4 per cent). The majority of them had herpes zoster and herpes simplex. Two patients with molluscum contagiosum came under our observation.

The eleventh and last group included the patients with vesiculobullous eruptions, a total of 12 (0.6 per cent). Of this number, 6 had extensive vesiculopustular lesions of undetermined origin, 5 had dermatitis herpetiformis and 1 had pemphigus vulgaris.

The 2,000 patients whose cases were analyzed and grouped into eleven diagnostic groups were made up of persons with eighty-four separate entities, considerably less than the one hundred and eighty-nine entities in Woolhandler's report on 3,000 cases. The discrepancies in these figures may be due to the larger number of cases analyzed by Woolhandler and probably to our adherence to the more general list of army diagnostic terms.

TREATMENT

Soldiers whose conditions allowed treatment while on duty were treated at the outpatient clinic. However, confinement to quarters was impossible for most of the patients owing to the poor facilities offered by camps, bivouacs and other temporary quarters. Thus, all patients requiring even the shortest periods of confinement to bed or extensive medication had to be hospitalized.

In the supply of drugs and bases there was very little variety, but the few items available through our pharmacy proved to be quite adequate in the treatment of all diseases with which I had to deal.

For wet dressings we employed potassium permanganate, boric acid, resorcinol, magnesium sulfate, silver nitrate and saline solutions. Bases obtainable were petrolatum, hydrous wool fat, zinc oxide paste, boric acid ointment, zinc oxide, talc, collodion and their combinations. Incorporated in these bases the following medicinal agents were used: precipitated sulfur, resorcinol, salicylic acid, crude coal tar and ammoniated mercury. For internal and parenteral medication, sulfadiazine, penicillin, calcium gluconate, oxophenarsine hydrochloride, bismuth and autogenous blood were used.

Bacterial infections reacted well to simple compresses of solution of boric acid, bactericidal pastes and a solution of gentian violet medicinal in combination with sulfadiazine taken internally.

We could not see any definite advantage of penicillin therapy for infectious dermatoses, although we have not had extensive experience with this drug as yet. Our impression was that the chronicity of impetigo and ecthyma may have been due not so much to the failure of topical medication and of sulfadiazine, as to inadequate bandaging, insufficient instructions and poor cooperation of the patient. Mercury ointments failed often, but if the same agent was applied in a thick absorbent paste the results were more satisfactory. When medicine such as sulfonamide drugs and penicillin failed, proper hygiene of the nails and rigorous bandaging, that is, prevention of reinoculation, helped to clear obstinate infections.

Patients with scabies were treated with two to three applications of benzyl benzoate in equal parts of medicinal soft soap and alcohol. After a shower and scrubbing, the scabicide was applied from the neck down, covering every inch of the body. Its advantage over the old sulfur therapy lies in the fact that, not containing any grease, it is not messy and is more comfortable to apply, especially for ambulatory patients. Regardless of what scabicide is applied, the results depend not so much on the agent used as on the method of application and on proper instructions given to the patients. Instructions as to changing underwear or clothes are not enough to prevent reinoculation. Jewelry worn, such as rings, wrist watches and identification tags, and also the insides of shoes were cleaned with alcohol after the last application of the scabicide. All clothes worn by the patient within two weeks prior to the onset of symptoms were disinfected or laundered. A large number of patients with scabies of many months' duration, who had persistently neglected these measures, came to our attention. In many instances, the lotion or ointment was applied only to the area of lesions and often i long periods, causing thereby a secondary de matitis and further aggravating the conditi which already had assumed a predominant pyodermic picture.

In all cases of pruritic, infectious, parasiti and fungous diseases, the patient's finger nail and toe nails were clipped short and cleanlines of his hands was stressed. In cases of fungous in fections, especially those of the hands and fee débridement was carefully carried out. Loos particles of skin, scales, crusts and tops of ves cles were removed, and corneous thickenings after preliminary preparation, were carefull pared off. In cases of acute trichophytosis, ho soaks, compresses and painting with 2 per cen aqueous solution of gentian violet medicinal gav satisfactory results, while ointments and kera tolytics were applied only in the chronic stage of the disease. Satisfactory response to treat ment in our experience depended not so much on the particular drugs applied as on the quality of nursing and general care.

We have seen some patients with "id" exacer bations, which in several instances could be trace back to indiscriminate application of salicyli acid ointments to ringworm infections. One o this group had a severe erythroderma, and an other had a reaction resulting in severe exfolia tive dermatitis. Both patients responded favor ably after administration of 250 cc. of plasma intravenously.

Psoriasis was managed by the Goeckerman therapy (combined use of coal tar ointment and ultraviolet radiation). As chrysarobin was not available, we had to rely largely on salicylic acid ointment and the rather messy coal tar ointment in the treatment of ambulatory patients. We had not seen any definite advantage in auto hemotherapy or arsenic combined with these treatments.

Lichen planus responded readily to injections of bismuth preparations in combination with topical keratolytics, but recurrences were noted.

We refrained from the use of sulfonamide ointments, creams and powders. Thus we avoided the combined internal and topical application of these drugs which, as often reported in the literature, has frequently resulted in untoward reactions. The 2 instances of generalized dermatitis which were encountered that could be traced to simultaneous administration of sulfonamide drugs internally and topically strengthened our preference for other topical remedies.

Often the success or failure in the treatment of infectious dermatoses is believed to be due to

use of some particular bacteriostat or bacteri-
ide. Medicines are therefore changed frequently,
nd recourse is taken to stronger and stronger
ncentrations. Our impression has been, how-
er, that speedier cures occur not so much as a
sult of the kind of medicinal agent applied but
s a result of its proper application plus adequate
rsing and emphasis on the prevention of re-
culation. Instructions as to hygiene and proper
anagement of lesions were given in each case,
nd patients were questioned persistently as to
e way they followed these instructions.

Early hospitalization of outpatients who could
t carry out satisfactorily the essential and
metimes comparatively simple treatments owing
their living conditions prevented eventual ag-
ravation of their ailments and led to a more rapid recovery, thereby saving valuable duty hours.

SUMMARY

Two thousand dermatologic patients were treated in a station hospital in Italy within a period of one year and their cases were analyzed. They were subdivided into eleven groups, and our statistical data for the groups were compared with those of other authors.

Problems of treatment under military conditions are discussed as well as the effect of military life on the relative incidents of cutaneous diseases.

It is felt that a report of this nature may prove of interest to medical officers in this and other theaters of operations and to civilian dermatologists.

FIXED BULLOUS ERUPTION DUE TO SULFATHIAZOLE

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A case of fixed bullous eruption following sulfathiazole therapy is reported, with results of some allergic studies. Only one reference [1] can be found to a case of a similar nature, and at present this article is unavailable to us.

REPORT OF A CASE

G. S., a Negro aged 33, appeared at the dermatologic outpatient department of the University Hospital on June 16, 1943, with ten to fifteen bullous lesions of two weeks' duration on the mouth, penis, trunk and extremities. These bullae varied from 1 to 4 cm. in diameter and were filled with a clear fluid. He stated

Fig. 1.—Fixed eruption due to sulfathiazole; lesions on glans penis.

that seventeen years previously he had suffered from an attack of gonorrhea. Four years before this admission he experienced another attack of the same disease, which was treated by his own physician with sulfanilamide over a period of four months. Three months prior to this admission, because of a gonococcic reinfection, the patient was given sulfathiazole by his physician, after which a bullous eruption developed. Shortly before his admission to this clinic, sulfathiazole was administered once more, and during the time of its administration the present eruption appeared. These lesions occupied precisely the sites where the bullae of the initial eruption had occurred. These facts were confirmed by communication with the patient's family physician.

Allergic Studies.—After the eruption had subsided, passive transfer tests of the Prausnitz-Küstner type were made. In addition, blisters were raised with cantharides on normal skin and on the sites of the previous lesions. Fluid from these was used for passive transfer tests in accordance with the technic described in a previous article.[2] The test material included blood and blister fluid, of which 0.1 cc. was injected into a nonsensitive person. Twenty-four hours later, a sulfathiazole solution was injected or a patch test with 5 per cent sulfathiazole in an oil in water

Fig. 2.—Fixed eruption due to sulfathiazole; sites of bullous lesions on glabrous skin.

emulsion base was applied. Sites of injections were read in one-half hour and forty-eight hours. The sites of patch tests were read in forty-eight hours. Appropriate controls were employed, and these included the injections of blood and blister fluids alone, blood and blister fluids plus isotonic solution of sodium chloride, the latter alone, sulfathiazole alone and 5 per cent sulfathiazole on a patch. All reactions were negative except to the test in which blister fluid was obtained from the sites of previous lesions (sites of fixed eruption) and into which a sulfathiazole solution was subsequently injected. Both immediate and delayed reactions at those sites were positive. It was noted that at the thirty

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1. Langhans, J.: Fixed Eruption Following Therapy, Dermat. Wchnschr. **115**:809-810 (Sept. 26) 1942.

2. Shaffer, B.; Lentz, J. W., and McGuire, J. A.: Sulfathiazole Eruptions: Sensitivity Induced by Local Therapy and Elicited by Oral Medication, J. A. M. A. **123**:17-23 (Sept. 4) 1943.

minute reading the control sites where sulfathiazole was injected showed some reactions. The reactions were, however, much smaller than one which appeared at an experimental site. The reactions at two control sites were no longer present when reexamined forty-eight hours later, while a definite positive reaction was read at an "experimental" site (an indurated papule 11 mm. in diameter).

COMMENT

While fixed eruptions to sulfanilamide have been reported,[3] to our knowledge this is the first report of a fixed bullous eruption due to sulfathiazole which we could substantiate. In a previous report,[2] we were able to demonstrate passive transfer of sensitivity by both blood and blister fluid in cases of generalized bullous and eczematous dermatitis due to sulfathiazole.

In this case, we have shown apparently by passive transfer with blister fluid that sensitivity to sulfathiazole exists in the sites of the fixed eruption but not in the normal skin. Loveman and Simon,[3a] using patch tests, have demonstrated in sensitivity to sulfanilamide a similar phenomenon.

SUMMARY

A case of fixed bullous eruption following sulfathiazole therapy for gonorrhea was observed and studied. This diagnosis was confirmed by passive transfer tests, blister fluid from the lesion sites of the fixed eruption being used. Blister fluid obtained from the normal skin in a patient with a fixed eruption of limited distribution due to sulfathiazole elicited negative reactions to passive transfer tests.

3. (*a*) Loveman, A. B., and Simon, F. A.: Fixed Eruption and Stomatitis Due to Sulfanilamide, Arch. Dermat. & Syph. **40**:29-34 (July) 1939. (*b*) Goodman, M. H., and Arthur, R. D.: Fixed Eruptions: Report of an Unusual Condition Due to Sulfanilamide, ibid. **43**:692-697 (April) 1941. (*c*) Fowlkes, R. W.; Pepple, A. W., and Vaughan, E. W.: Cutaneous Reactions Due to Sulfanilamide, South. M. J. **35**:1015-1016 (Nov.) 1942.

TREATMENT OF DERMATOSES WITH VASODILATORS

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An adequate supply of available oxygen is essential to the normal functioning of the cells of the body. Oxygen inadequacy may be localized to a small area so that local tissue anoxia may exist without anoxemia. Hippocrates more than two thousand years ago said: "So in one place the blood stops, in another it passes sluggishly, in another more quickly. The progress of the blood through the body proving irregular, all kinds of irregularities occur." Petersen [1] has proved the validity of these words by showing experimentally that variation in the oxygen supply to the tissues is a common event. He believes that dysfunction of the mechanism which has to do with oxygen supply is probably the fundamental cause of disease. This report deals with results obtained in a series of patients afflicted with cutaneous diseases who were subjected to treatment designed to increase the oxygen supply of the skin.

There are many causes for interference with the normal flow of blood to the tissues. Spasm of the arterioles is an important and frequent one. Epinephrine, nicotine, histamine, emotion, cold, bacteria and alkalosis are some of the causes of vasoconstriction. Moon [2] has demonstrated that the normal capillary endothelium allows water and crystalloids to pass into the tissue, but when the arterioles are constricted, with resulting anoxia, the capillaries dilate and become permeable to blood cells, colloids and plasma proteins. The resultant hyperemia evidenced microscopically by vascular dilatation with perivascular cellular infiltrate is found so frequently in the early stages of many dermatoses that a vascular dysfunction underlying these diseases may be surmised. Banks [3] believes that scleroderma, dermatomyositis, disseminated lupus erythematosus, Libman-Sacks syndrome and polyarteritis nodosa are all diffuse vascular diseases.

Nedzel [4] demonstrated that arteriolar spasm, although only transient in character, deprives the tissue supplied by that particular blood vessel of oxygen to such an extent that alterations are seen microscopically. These consist of dilated capillaries, perivascular edema and round cell infiltration with changes ranging from simple hyperemia to necrobiosis. His photographs clearly show the effect of vascular spasm on the tissues. The capillaries become permeable to colloids. Bacteria and other particulate matter adhere to the swollen endothelium. Anoxia is "patchy" in character and occurs only in areas showing vascular damage and not in tissue only a few centimeters distant. The lesions of lupus erythematosus on the face, where sunlight may be a precipitating factor, is an example of this. Sunlight not only destroys material in the skin necessary for normal function, such as riboflavin, but it may liberate histamine which in turn damages the small blood vessels and leads to permanent abnormalities in the local circulation, thus favoring the localization of bacteria.

The clinical symptoms and pathologic findings in a number of cutaneous diseases present a picture of vascular spasm. This occurs most readily in persons whose vascular system is unstable, as in the leptosome type of person. Given such a person, any one of several factors, such as infection, fatigue, emotion and meteorologic alterations,[5] may easily lead to vasospasm and cutaneous disease. In other words, autonomically stable persons are able to preserve their functional equilibrium in spite of a sudden chilling, but let a person not so constituted be exposed to the same trauma and vasospasm will occur in "susceptible" tisues. Such tissues are the ones that have been previously damaged by excessive sunlight or infection and occur most readily in organs possessing terminal vessels, such as the eye, brain, kidney and skin. Experiments show that the oxidation-reduction potential of the skin varies greatly in different areas, as in

From the Northwestern University Medical School, Department of Dermatology, and the Outpatient Department of Grant Hospital.

1. Petersen, W. F., and Milliken, M. E.: The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, Inc., 1934.

2. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

3. Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:433 (Sept. 18) 1941.

4. Nedzel, A. J.: Vascular Spasm, Urbana, Ill., University of Illinois Press, 1943.

5. Schmidt, F. R.: Skin Diseases and the Weather, Arch. Dermat. & Syph. **32**:781 (Nov.) 1935.

the flexor surfaces compared with the extensor surfaces.[6] This difference in oxygen requirement may be relative, for it is the disparity between the need for oxygen and its available supply that is the determining factor. Wherever local anoxia or increased metabolism or both prevail localization of lesions may occur.

For a few years I [7] used iodine therapeutically in an attempt to overcome vasospasm and improve the circulation of the skin. Vasodilatation with improved tissue oxidation was obtained in some early cases of psoriasis, alopecia areata and pruritus. I wish to stress the importance of treating these diseases early in their course, for later pathologic changes in the tissues exclude the possibility of returning the cells to normal.

During the past year I have treated 55 patients with diseases of the skin with substances that induce vasodilatation. These included nicotinic acid, nicotinamide, acetylcholine, sodium nitrite, erythrityl tetranitrate, typhoid vaccine and estrogen. Following the advice of Duggan [8] and Cordes,[9] who secured excellent results with these drugs in a number of ocular diseases, patients are forbidden to use tobacco and exposure to cold is to be avoided, as should also psychic trauma, worry and excitement. One teaspoon of cider vinegar in one-half glass of water, three times daily, is also prescribed. Nicotinic acid in doses of 50 to 100 mg. three times daily proved effective and economical and was therefore used in the majority of cases. It should be given with meals to avoid excessive flushing and tingling of the skin. Sodium nitrite intravenously in 100 mg. doses was used in acute cases of purpura and erythema multiforme with good results.

Determinations of blood pressure were made whenever possible.

TABLE 1.—*Summary of Data on Patients with Dermatoses Treated with Vasodilators*

Disease	Average Duration of Disease	Number of Cases	Results	Comment
Psoriasis	5 years	6	Unimproved	No early cases encountered in this series
Itching of legs with peripheral vascular disease	6 months	8	Improved	
Summer prurigo	2 years	2	Rapid improvement	
Erythema multiforme	1 day to 3 weeks	7	Rapid improvement	Lesions disappeared quickly
Toxic erythema from drugs	2 days	3	Rapid improvement	Itching stopped promptly
Urticaria	3 days to 4 years	8	Improvement in early cases only	
Pityriasis rosea	6 days after appearance of generalized eruption	4	Rapid involution of lesions in 1 case of 2 days' duration	
Purpura	5 days	2	Rapid improvement	
Erythema nodosum	1 week	2	Rapid improvement	
Alopecia areata	2 months	2	Hair stopped falling out	
Herpes simplex	3 days	5	Undetermined	
Herpes zoster				
Lupus erythematosus	3 years	4	Undetermined	No disseminated cases were treated
Cold allergy	2 years	1	No attacks while taking nicotinic acid	
Dermatitis herpetiformis	3 years	1	Improvement	Itching controlled

COMMENT

The results observed with this therapeutic modality are encouraging, provided that treatment is instituted early in the course of the disease. The rapid involution of so-called inflammatory dermatoses such as purpura, summer prurigo, erythema multiforme, erythema nodosum and toxic erythema was striking and should stimulate the employment of these drugs by those who may have the opportunity to study early instances of scleroderma, dermatomyositis, disseminated lupus erythematosus, acrodermatitis atrophicans and angioneurotic edema. In addition, I believe that erythrocyanosis of the legs in young girls and in some cases cold allergy and pityriasis rosea might react favorably to vasodilators.

These studies suggest the possibility of securing better penetration into the skin of a substance like a gold compound as used in the treatment of lupus erythematosus. Chambers and Bernton [10] have recently found that patients with urticaria were more promptly relieved of symptoms if calcium gluconate was administered in conjunction with nicotinic acid.

Lately, I have found that the administration of other water-soluble vitamins such as thiamine

6. Schmidt, F. R.: Blood and Oxygen Supply of the Skin, Arch. Dermat. & Syph. **32**:576 (Oct.) 1935.

7. Schmidt, F. R.: The Action of Iodine on Diseases of the Skin as Influenced by Season and Weather, Arch. Dermat. & Syph. **42**:1083 (Dec.) 1940.

8. Duggan, W. F.: Clinical Vascular Physiology of the Eye, Am. J. Ophth **26**:354 (April) 1943.

9. Cordes, F. C.: The Use of Vasodilators in Acute Fundus Disease, Am. J. Ophth. **26**:916 (Sept.) 1943.

10. Chambers, D. C., and Bernton, H. S.: The Administration of Nicotinic Acid and Calcium Lactate in Urticaria, J. Allergy **15**:141 (March) 1944.

and riboflavin along with nicotinic acid appears to augment the beneficial effects of nicotinic acid alone. This may be explained by recalling that thiamine acts by potentiating the action of acetylcholine, the vasodilator hormone of the body. Moreover, nicotinic acid, thiamine and riboflavin apparently play an important role in the oxidation of carbohydrate in the central nervous system.

The rapid involution of certain lesions observed in this series of patients when nicotinic acid was administered finds corroboration in the work of other investigators. Bean, Spies and Vilter [11] reported that pellagrous dermatoses disappear quickly following oral administration of nicotinic acid.

It is suggested that persons suffering from livedo reticularis with ulcerations be subjected to vasodilator treatment, in lieu of sending them to a place of high altitude and low barometric pressure.

SUMMARY

Results obtained with vasodilators in the treatment of 55 patients afflicted with diseases of the skin suggest their further employment in a large series of cases. The most favorable response to vasodilators was observed in dermatoses characterized by so-called inflammatory lesions, thus substantiating the assumption of their arteriolar-capillary origin.

122 South Michigan Avenue.

11. Bean, W. B.; Spies, T. D., and Vilter, R. W.: Asymmetrical Cutaneous Lesions in Pellagra, Arch. Dermat. & Syph. **49**:335 (May) 1944.

PIGMENTATION OF HAIR ON TRANSPLANTED SKIN IN HOODED RATS

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While making some studies on the pigmentation of hair in piebald rats and exchanging areas of skin producing black hair with areas having white hair, my colleagues and I noted that the skin which formerly grew black hair often produced white hair in its new environment. In other rats areas of skin producing black hair were then incised and sutured back in their original sites, and they often produced white hair. The latter experiments showed that the white hair on the transplants was due to changes resulting from the operation rather than to the environment.

These results differed from the observations made on guinea pigs by Seevers and Spencer,[1] who found in 52 sucessful grafts that transplantation of skin from a colored area to a white area showed that the hair follicles do not lose their pigment-producing potentialities in an unpigmented area. Lewin and Peck,[2] in similar experiments on guinea pigs, found that dark skin transplanted to a white skin area usually produced no hair. Any hair that was present on the graft or was regenerated retained the characteristics and color of the original site. However, in some instances, white hair of poor quality developed in the center or was scattered through the graft.

The skin of hooded rats differs from the skin of guinea pigs. Unpigmented skin produces black hair in rats, while black hair grows in pigmented skin in guinea pigs. The skin of a hooded rat is, therefore, quite comparable to the skin covering the head of a white man.

To determine whether or not the white hair on the transplanted skin and the incised skin was due to a disturbance of the vascular or of the nervous relations, areas of skin producing black hair were denervated in some animals. All observations indicated that the white hair resulted from depriving the skin of its vascularity.

By following the growth of the hair for several cycles[3] on the transplanted and the incised areas, it was evident that the cells of the hair bulbs were unable to regain their ability to form pigment once they had lost it.

The descriptions of the grafts and the conditions which have induced the white hair and which may be responsible in many instances for the graying of hair in mammals with age are of such interest that they seem to warrant reporting.

EXPERIMENTAL PROCEDURE

Piebald rats of the Long-Evans strain were used in these experiments. When the animals were 22 days old, the hair was removed from a region producing black hair and a region producing white hair with sodium sulfide.

With the animals under ether anesthesia areas of skin, approximately 0.75 cm. square and thick enough to include the panniculus carnosus, were incised and then interchanged between the regions. The grafts were held in place with interrupted sutures and coated with petrolatum to prevent drying, as in previous transplantation experiments.[4] Twenty-five such interchanges were made, and in 19 instances both transplants survived. The grafts usually persisted if they had a white pinkish color seventy-two hours after the interchange.

When the next growth of hair appeared externally on the grafts, usually about the age of 38 days,[5] many gradations in pigmentation and in quality of the hair existed on the areas which formerly produced black hair. These grafts will now be described.

Figure 1 shows a transplant covered almost entirely with fine white hairs except for the few black hairs around the periphery of the graft. The area of this graft has enlarged slightly since the time of transplantation.

From the Departments of Anatomy, College of Dentistry and the Graduate School of Arts and Science, New York University.

1. Seevers, C. H., and Spencer, D. A.: Autoplastic Transplantation of Guinea Pig Skin Between Regions with Different Characters, Am. Naturalist **66**:183-189, 1932.

2. Lewin, M. L., and Peck, S. M.: Pigment Studies in Skin Grafts on Experimental Animals, J. Invest. Dermat. **4**:482-505, 1941.

3. Butcher, E. O.: The Hair Cycles in the Albino Rat, Anat. Rec. **61**:5-19, 1934.

4. Butcher, E. O.: Hair Growth on Skin Transplants in the Immature Albino Rat, Anat. Rec. **64**:161-171, 1936; Fate and Activity of Autografts and Homografts of Skin in White Rats, Arch. Dermat. & Syph. **36**:53-56 (July) 1937.

5. Butcher, E. O.: Hair Growth in Adrenalectomized, and Adrenalectomized Thyroxin-Treated Rats, Am. J. Physiol. **120**:427-434, 1937.

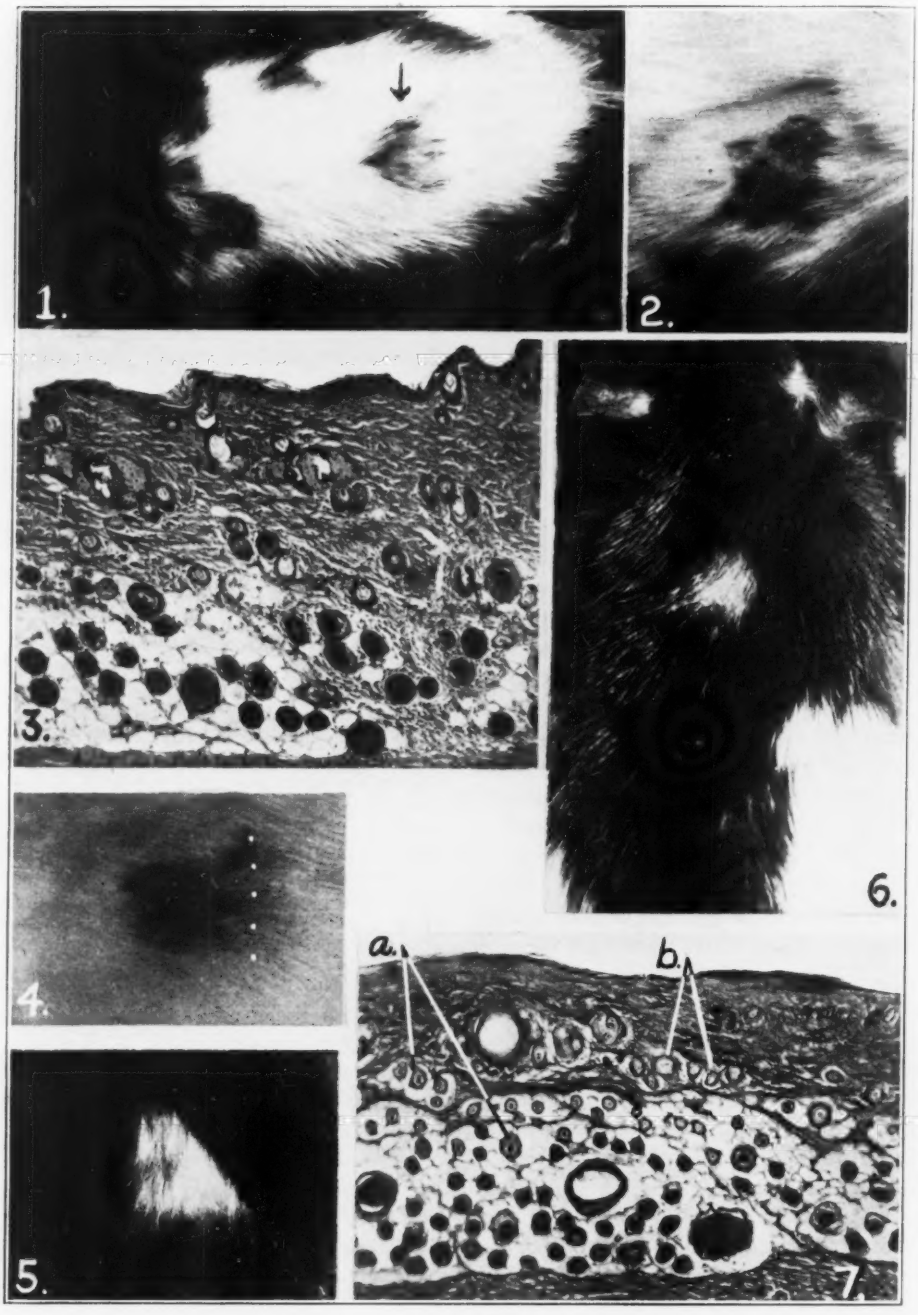

Fig. 1.—An area which formerly produced black hair now has fine white hairs.

Fig. 2.—This graft has a band of white hair.

Fig. 3.—A histologic section of the graft shown in figure 2. On the right side of the photograph dense and cellular tissue is associated with white hairs. × 80.

Fig. 4.—The anterior part of this graft is producing black hair while the posterior part has white hair. The dotted line marks the posterior limit of the graft.

Fig. 5.—An area was incised and sutured back in this hooded rat, and it produced white hair.

Fig. 6.—This photograph shows an area which was incised and sutured in the original site.

Fig. 7.—A histologic section of the left side of the graft shown in figure 5. Black hairs (*a*) are on the left and white hairs (*b*) on the right side. × 70.

In figure 2 is seen a graft which enlarged from the time of transplantation and which has a band of white hair running through it. All the hairs on this graft are coarse and good in quality. The hair has been cut away around the graft to show the extent and condition of the transplant. Figure 3 shows a histologic section through the graft. Associated with the white hairs on the right side of the photograph is a dense and cellular subcutaneous tissue which has replaced the loose fatty tissue. It seems possible that this dense tissue may in some way be responsible for the failure of follicles in this region to produce pigment. While dense tissue is sometimes found associated with the lack of pigmentation, cases are equally common in which there are no changes in the subcutaneous tissue and yet a lack of pigmentation exists.

Figure 4 shows a graft which has enlarged considerably since the time of interchange. The anterior part of this graft is producing black hair while the posterior part, the posterior limit of which is indicated with a dotted line, has white hair. The quality of the hair on the two parts is similar. The animal bearing the graft shown in figure 4 was killed, and its vascular system was injected with india ink. The transplant and the surrounding skin were then fixed in Bouin's fluid, cleared and spread on a slide. Tracings of the vascular channels were made with a projector, and no differences in the vascular supply of the two parts could be found. Histologic sections of the two parts also were very similar, and no differences in the distribution of collagenous and elastic fibers, in the amount of adipose tissue or in the structure of blood vessels could be found which would account for the lack of pigmentation. Histologic sections of grafts from other rats confirmed these observations.

In the previous experiments there existed the possibility that the region surrounding the transplanted area in some way induced the lack of pigmentation.

To test this possibility, areas of skin were completely incised in regions producing black hair and then sutured back in their original positions. Rats 22 days old with hair follicles in the resting stage were again used for these experiments. Figure 5 shows a typical result of such an operation in a hooded rat. The graft has enlarged since the operation and is producing white hair of good quality. No histologic differences exist in sections (fig. 7) taken at the junction of the incised skin with the surrounding skin. The result of a similar operation on a piebald rat is seen in figure 6. In this instance there has been a shrinkage of the incised area, which is producing white hair of good quality.

One might have thought that the cells would have recovered their pigment-forming potentialties with the establishment of the blood supply and would have again produced black hair. This was, however, not the case, for the incised areas and grafts on the piebald animals continued to produce white hair in the successive hair cycles.[3]

Irritants (xylene, benzoic acid and capsicum) were applied daily to some of the transplanted areas to determine whether increased vascularity and an edematous condition would induce the cells of the hair bulbs to form pigment again. No increased pigmentation resulted in the successive growth cycles. Lewin and Peck [2] also failed to increase the pigmentation of guinea pig skin with applications of ultraviolet rays. Pantothenic acid, the antigraying factor [6] in rats, was dissolved in Pentrasol A [7] (60 mg. of calcium pantothenate to 5 cc. of Pentrasol A) and applied to the grafts producing white hair during the successive cycles, and no increased pigmentation resulted.

There existed the possibility that the lack of nerve supply was responsible for the lack of pigmentation in these incised areas, since interference with the nerve supply has been associated with the depigmentation of skin in leprosy.[8] To test this possibility incisions were made through the skin (including the panniculus carnosus) on each side of the body from the middle of the axilla anteriorly to the thigh posteriorly. A scalpel was then inserted under the skin (beneath the panniculus carnosus), and all the branches of the spinal nerves and peripheral blood vessels were sectioned to this large region of skin over the dorsum of the rat. The incisions were sutured, and they quickly healed. Blood was then supplied to the dorsal region from anterior and posterior vascular channels, which were seen to hypertrophy quickly. No necrotic areas resulted in this large region, and the usual pattern of pigmented hair appeared with the cyclic growth over the back.

Some sympathetic nerves possibly coursed along with the blood vessels into this dorsal region, and some investigators might claim that the region was not entirely denervated. It

6. Emerson, G. A., and Evans, H. M.: Growth and Graying of Rats with Total "Filtrate Factor" and with Pantothenic Acid, Proc. Soc. Exper. Biol. & Med. **46:** 655-658, 1941.

7. Herrmann, F.; Sulzberger, M. B., and Baer, R. L.: New Penetrating Vehicles and Solvents, Science **96:** 451-452, 1942. Pentrasol A consists of 20 Gm. of Aerosol MA and 20 cc. of xylene warmed under reflux until a glassy gel results. This gel is taken up with 20 Gm. of antipyrine and 80 cc. of propylene glycol.

8. Boyd, W.: A Textbook of Pathology, ed. 4, Philadelphia, Lea & Febiger, 1943.

would seem, however, that such incisions would have had some effect on the pigmentation if the nerves were responsible for the lack of pigmentation in the new growth of hair. The rats had no sensation in this dorsal region which had been incised laterally. If the lack of nerves were responsible for the absence of pigmentation, it would be difficult to explain the presence of patches of black hair completely surrounded by white hair on some of the transplanted areas. In these cases the nerves in all probability would grow in from the periphery and the pigment-forming cells would be more apt to survive in the periphery than in the center of the graft.

Thus there was no evidence that the lack of nerves was associated with the lack of pigmentation.

The areas on which white hair normally grew and which were transplanted into regions producing black hair continued to produce white hair of a variable quality.

SUMMARY

When skin producing black hair is interchanged with skin producing white hair in the piebald rat, white hair frequently grows on the skin which formerly had black hair. Likewise, if skin producing black hair is incised and sutured back in place, it often produces white hair.

The present conception of pigment formation seems to be that pigment results from the combination of a chemical substance, or propigment, carried by the blood with an enzyme in the cells of the hair bulb. In these rats the propigment was present, since the rest of the hair of the animal remained black and black hairs often appeared among the white ones on the grafts. The white hair was not due to the lack of innervation, as was shown by denervating areas. The enzymatic potentialties of the cells of the hair bud must, therefore, have been affected by the lack of vascularity and nutrition immediately following the operation, since injection studies show that the vascular supply of the graft soon becomes similar to the supply of the surrounding skin.

Once the pigment-forming ability is lost by the cells, there is no restitutive capacity. Application of irritants to the skin has failed to induce the cells of the hair buds to form pigment again.

Growth or production of the hair by the hair bud is also affected by vascularization. Increased blood supply accelerates hair growth.[9] Growth is not affected permanently by poor blood supply, as shown in these experiments, while the pigment-forming capacities of the cells are affected permanently.

When the skin was incised, all blood supply was eliminated. Nutrition was supplied to the graft by tissue fluid from below the graft and from around its periphery. This tissue fluid sufficed to supply the cells of the hair bulb with nutrition necessary for the survival of their growth potentialties. The tissue fluid, however, did not provide the cells with the substances necessary for the survival of their enzymatic potentialties. Thus, the requirements for growth are less than for pigment formation.

9. Butcher, E. O.: The Effects of Irritants and Thyroxin on Hair Growth in Albino Rats, Am. J. Physiol. **129**:553-559, 1940.

LICHEN SCLEROSUS ET ATROPHICUS IN CHILDHOOD

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Lichen sclerosus et atrophicus is ordinarily a disease of adults. It occurs most frequently in middle-aged women, although no relationship to the menopause has ever been established. The observation of 3 cases of lichen sclerosus et atrophicus in young girls within a short period is noteworthy and constitutes the basis of this report.

CLINICAL FEATURES

Within the past fifteen years there have been two detailed discussions in the American literature concerning lichen sclerosus et atrophicus and related disorders such as guttate morphea and atrophic lichen planus, that of Nomland [1] in 1930 and that of Montgomery and Hill [2] in 1940. These observers have done a good deal to clarify the utter confusion which previously existed in connection with these diseases, especially as to terminology. Montgomery and Hill were correct in urging the abandonment of the terms "white spot disease" and "card-like scleroderma of Unna" which were used loosely to include both morphea and lichen sclerosus atrophicus. Lichen albus of Zumbusch and chronic atrophic lichenoid dermatitis of Csillag are terms which have also been used to describe lichen sclerosus et atrophicus. It is the consensus now that the disease is not a form of atrophic lichen planus, so that the terms lichen planus sclerosus or lichen planus sclerosus et atrophicus are obsolete and no longer acceptable in modern nomenclature.

The primary lesion in lichen sclerosus et atrophicus is an achromatic, irregular or polygonal flat papule. In well developed cases the individual papules coalesce to form ivory-colored plaques of various sizes and shapes, although in many cases both the plaques and the individual papules may be seen. The lesions may be on the same plane as the neighboring normal skin or slightly elevated. Most typical lesions present tiny comedolike plugs studding their shining and otherwise smooth surfaces, although such follicular plugs are not absolutely essential to the clinical diagnosis. Even when they are not obvious grossly, however, they may be seen in microscopic sections. Delling of the lesions may be present, and in old patches of the disease the skin may be atrophic, resembling parchment.

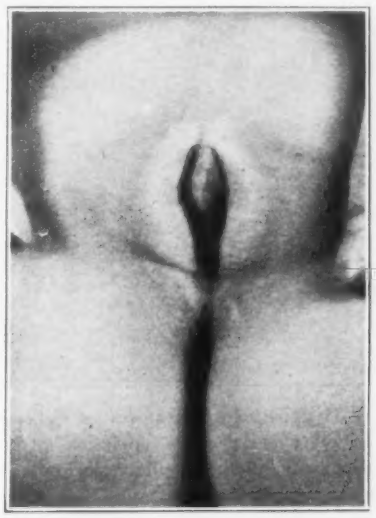

Fig. 1.—Lichen sclerosus et atrophicus with involvement of the vulva and perianal region in a girl aged 4½ years.

The favorite sites of involvement are the upper parts of the trunk, especially the sternal and clavicular areas, the neck, axillas, forearms and anogenital region. The disease is commonly limited to the vulva and perianal areas. It is the opinion of Freeman and me [3] that lichen

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1. Nomland, R.: Lichen Sclerosus et Atrophicus (Hallopeau) and Related Cutaneous Atrophies, Arch. Dermat. & Syph. **21**:575 April) 1930.

2. Montgomery, H., and Hill, W.: Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **42**:755 (Nov.) 1940.

3. Freeman, C., and Laymon, C. W.: Balanitis Xerotica Obliterans, Arch. Dermat. & Syph. **44**:547

(Footnote continued on next page)

sclerosus et atrophicus can likewise occur on the male genitals as isolated papules on the shaft and/or sclerotic preputial and urethral involvement. Both types of genital involvement may occur alone or with lesions elsewhere on the body. Cases of this type have usually been reported under the title balanitis xerotica obliterans.

The disease is a rarity in the young. In Montgomery and Hill's large series of 46 cases,

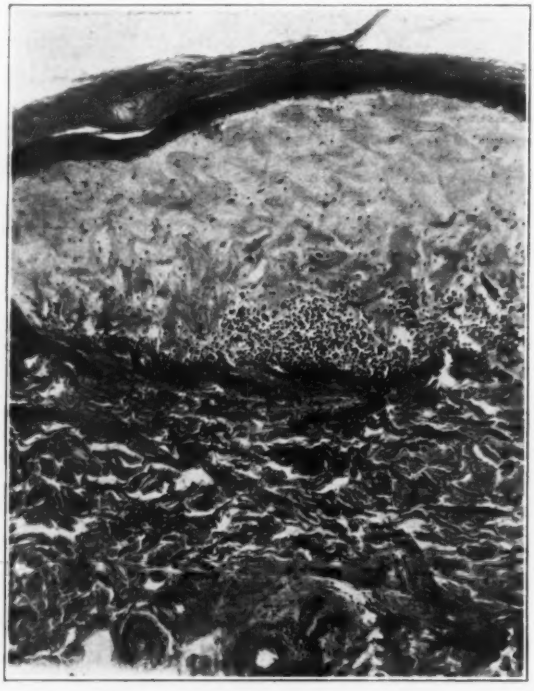

Fig. 2.—Histopathologic features of lichen sclerosus et atrophicus: hyperkeratosis, epidermal atrophy, zone of homogenization in the papillary portion of the cutis and zone of lymphocytic infiltration beneath.

only 1 began in a girl aged 10. There were 3 cases in patients in the late twenties, 4 in persons in the thirties and all of the rest occurred in patients in the fourth to the seventh decades of life. Many dermatologists were questioned, but none could remember seeing a case in early childhood.

Regardless of age of onset the course of the disease is long and treatment is of no avail. The cause is unknown.

(Oct.) 1941. Laymon, C. W., and Freeman, C.: Relationship of Balanitis Xerotica Obliterans to Lichen Sclerosus et Atrophicus, ibid. **49**:57 (Jan.) 1944.

HISTOPATHOLOGIC FEATURES

Well developed lesions of lichen sclerosus et atrophicus have histopathologic features which are pathognomonic. Perhaps the most striking is the band of homogenization directly beneath the epidermis. Montgomery and Hill regarded this as lymphedema rather than true sclerosis in the sense that there is a true increase in connective tissue. The elastic fibers are split but not destroyed. Beneath the homogenized area in most cases is a bandlike zone of lymphocytic infiltration. This feature is not present in all cases, and in early lesions the infiltrate may be situated only about dilated blood vessels. Obliterative changes of the deep vessels, as seen in scleroderma, are not present in lichen sclerosus et atrophicus.

The epidermal changes consist of hyperkeratosis, keratotic plugging of the follicles and atrophy of the rest of the epidermis with flattening of the rete pegs. There may be vacuolization and mild liquefaction degeneration of the basal layer.

REPORT OF CASES

Case 1.—B. P., a white girl aged 6 years, was first seen in February 1943. Her mother had noted lesions on the child's vulva about fifteen months previously, shortly before her fifth birthday.

On examination there were achromatic, sclerotic plaques surrounding the vulva and extending posteriorly over the perineum to the anus but not encircling it. The labia minora appeared shrunken. There were several fissures on the surface of the lesions on the perineum. There were no other abnormalities on the rest of the skin or mucous membranes.

A biopsy was performed, and the histopathologic changes confirmed the clinical diagnosis of lichen sclerosus et atrophicus.

The child was reexamined at approximately monthly intervals until October 1944. After a trial of arsenic therapy (asiatic pills) and vitamin A orally with bland lubricating ointments topically there was moderate improvement. At the time of the last examinations the affected skin was somewhat more pliable, and there have been no fissures for several months.

Case 2.—S. D., a white girl aged 4½ years, was first seen in December 1944. Lesions about the vulva had been present for one month. For the same period the child had complained of difficulty and discomfort at the time of defecation.

On examination the vulva and perianal region appeared to be surrounded by a zone of depigmentation. On palpation, however, it was obvious that the ivory-colored areas were inflexible and somewhat sclerotic. There were no other lesions on the body.

The histopathologic changes confirmed the clinical diagnosis of lichen sclerosus et atrophicus.

The child was given vitamin A orally and a lubricating ointment, and when she was again examined three and one-half months later the appearance seemed unchanged although there was no discomfort at the time of defecation.

CASE 3.—S. W., a white girl who had just passed her fourth birthday, was seen in June 1945. Yellowish white areas were first noted in the perianal region three months previously.

Examination showed lesions on the vulva, perineum and perianal region practically identical with those in the previous 2 cases. There were several fissures and erosions about the anus. Numerous telangiectatic blood vessels coursed over the slightly shriveled labia minora. The rest of the skin was normal.

The histopathologic changes were consistent with the clinical diagnosis of lichen sclerosus et atrophicus.

The patient has not reported for subsequent examination.

SUMMARY

Lichen sclerosus et atrophicus, although predominantly a disease of middle-aged women, can occur in young children. In 3 cases in girls below the age of 6 years the lesions were limited to the anogenital region.

DIFFERENTIATION OF LEPROMATOUS FROM "NEURAL" LEPROSY

THE BASIS, A METHOD, AND REPORT OF FIVE CASES

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The diagnosis of leprosy should in most cases permit a prognosis to be made as well. This offers three important advantages to the physician: It enables him to decide on the disposition of the case, whether to isolate or merely observe; it permits him to evaluate the effect (if any) of treatment; and it permits him (if it is favorable) to soften the blow when he informs the patient of the diagnosis.

These advantages can be accomplished only by making an exact diagnosis: that is, not merely "leprosy," but "leprosy, lepromatous," or "leprosy, 'neural'." Lepromatous leprosy has a bad prognosis for arrest or recovery; "neural" leprosy has a good prognosis for arrest or recovery. It is rare for the disease to undergo transition from either type to the other, and it is probably impossible for a patient to present both types simultaneously. The term "mixed leprosy" was never intended to mean *mixed types* of the disease; it really means lepromatous leprosy in *mixed sites of involvement*—both skin and nerves. Inasmuch as virtually every patient with leprosy of whatever type presents lesions of both the skin and the nerves, the term is an unnecessary and confusing one, and should be abandoned.

This basic distinction between the two types of leprosy can usually be made without difficulty, even in comparatively early cases, and it is with this differentiation that this paper will be primarily concerned.

LEPROMATOUS LEPROSY

Lepromatous leprosy is the form of the disease once known as elephantiasis, leontiasis, or satyriasis, Graecorum. Avicenna is said [1] to have suggested that the first two of these names stemmed from the fearful and terrifying appearance of the facies in advanced cases. Aretaeus, too, said the name elephantiasis was applied to leprosy because it was "disgusting to the sight, and in all respects terrible, like the beast of similar name." More recent synonyms for this form of leprosy are "tubercular leprosy" (i. e., leprosy characterized by tubercles or nodules) and "cutaneous leprosy"; the latter term was the official one from 1931 to 1938, being adopted because of the tendency of this form of the disease to involve the skin somewhat more conspicuously, in most cases, than the nerves.

Lepromatous leprosy is characterized primarily by red, elevated, granulomatous infiltrations of the skin which are called lepromas (fig. 1). More diffuse infiltrations may also occur. These lesions are typically rich in Mycobacteria leprae, and are never free from them except perhaps in the transitory earliest stages or in advanced retrogression. These granulomas occur in the skin, in nerves and in virtually all of the reticuloendothelial structures of the body—lymph nodes, testes, bone marrow, liver and spleen. Mitsuda [2] has observed lepromatous infiltration also in the heart, stomach, intestine.

Fig. 1.—Typical "lepromas" of helix and antitragus of ear. Below the ear is seen a swelling caused by acute lepromatous neuritis of the right great auricular nerve.

Read at the Annual Meeting of the California State Medical Association, Los Angeles, May 6, 1945.

1. Avicenna, in Bateman, T.: A Practical Synopsis of Cutaneous Disease, ed. 1, Philadelphia, Collins & Croft, 1818.

2. Mitsuda, K., and Ogawa, M.: A Study of One Hundred and Fifty Autopsies on Cases of Leprosy, Internat. J. Leprosy **5**:53 (Jan.-March) 1937.

kidney, urinary bladder, ovary and other sites. The conjunctiva, cornea, nasal mucous membrane, pharynx and larynx are also frequently involved in advanced cases. The cutaneous lesions of early lepromatous leprosy resemble urticaria more regularly and more closely than they do any other one disease; they rarely manifest hypopigmentation or annular configuration; and when advanced they frequently mimic with remarkable fidelity the clinical appearance of lymphoblastoma of the skin, either the nodular or the diffusely infiltrative type.

Neurologic changes are present in virtually every case of lepromatous leprosy. As in "neural" leprosy, these may vary from anhidrosis, thermal anesthesia, dermographism or alopecia (chiefly of eyebrows), through total anesthesia and muscular weakness, to muscular paralysis and atrophy and contracture, trophic absorption of bone and trophic ulceration. Cutaneous nerve damage in lepromatous leprosy, unlike that in "neural" leprosy, has no particular tendency to occur in the skin overlying the leprous cutaneous lesions, or to coincide in extent with such lesions; this occurrence is infrequent enough to be attributed to coincidence.

The other clinical manifestations of lepromatous leprosy—ocular and laryngeal involvement—are seen only in advanced cases; they eventuate in, respectively, blindness and laryngeal stenosis, the latter requiring tracheotomy.[3] Enlargement of the lymph nodes seldom attracts attention, and the other visceral lesions rarely if ever reach the clinical threshold. A notable exception to this is amyloid disease, which is regularly found at autopsy in the kidneys, liver and spleen, and apparently explains a large proportion of the deaths from "chronic nephritis," which is the assigned cause of death in about one sixth of most series of cases. In Hawaii, at least, it is felt that this is not the result of the frequently associated tuberculosis, for it is almost never seen in autopsies on nonleprous patients at the Leahi Hospital for tuberculosis in Honolulu.[4]

Histologically, the lesions of lepromatous leprosy consist of diffuse granulomatous infiltration composed of round and spindle-shaped histiocytes which are often loaded with fat and almost always with Myco. leprae (fig. 2). Their cytoplasm is foamy; some of them are vacuolated, and a few are multinucleated. The general appearance closely simulates that of xanthoma tuberosum. In nerves, there is typically only a sparse inflammatory infiltrate with fairly numerous vacuolated cells, and large numbers of bacilli. The relative lack of inflammatory reaction is in striking contrast to the picture seen in the nerves in "neural" leprosy, and suggests that permanent damage to an involved nerve might be expected to occur less often in the lepromatous form of the disease than in the "neural" form. Tilden[4] has recently reviewed lepromatous leprosy thoroughly from the histologic standpoint.

The lepromin (Mitsuda) test is regularly negative in lepromatous leprosy. This test consists of the intradermal injection of 0.1 cc. of a phenolized suspension of heat-killed Myco. leprae in isotonic solution of sodium chloride. This is usually prepared by grinding an amputated lepromatous ear lobe in a mortar with saline solution; the resultant suspension is filtered, autoclaved and phenolized. A positive reaction to the test consists of an elevated, infiltrated, erythematous papule 1 cm. or so in diameter, which frequently ulcerates at the center. The mature reaction usually requires about three weeks to develop.

Positive reactions to serologic tests of the blood for syphilis occur, according to Hopkins and Faget,[5] in 56.4 per cent of cases of "mixed" leprosy and in 60.2 per cent of cases of lepromatous leprosy without severe nerve damage. The close correspondence of these figures with one another is additional evidence of the futility of establishing separate categories for lepromatous cases with and without "marked" nerve damage. These authors also confirmed Badger's statement[6] that the proportion of positive reactions was higher among patients with active leprosy, particularly in those undergoing a lepra reaction.

Lepromatous leprosy is characterized by the occurrence at irregular intervals of the lepra reaction. This phenomenon consists of fever, neuralgia and erythema multiforme; the last usually takes the form of either severe erythema nodosum or, less frequently, erythema multiforme bullosum. Such lepromatous lesions as are already present are likely to become swollen and more erythematous, and often ulcerate. New lesions may appear. The sedimentation rate increases. The patient is acutely ill, and remains so for a variable period, usually a few weeks. He then gradually recovers from the

3. Sloan, N.: Tracheotomy in Leprosy, Internat. J. Leprosy, to be published.

4. Tilden, I. L.: Lepromatous Leprosy: A Reticuloendothelial Disease, Am. J. Clin. Path. **15**:165 (May) 1945.

5. Hopkins, R., and Faget, G. H.: Recent Trends of Leprosy in the United States, J. A. M. A. **126**:937 (Dec. 9) 1944.

6. Badger, L. F.: Significance of Positive Wassermann and Kahn Reactions in Leprosy, Pub. Health Rep. **46**:957 (April 24) 1931.

reaction, and returns to about the same condition in which he was before it occurred. Individual lesions may look somewhat improved, but his general condition is usually worse, and his

The prognosis of lepromatous leprosy is poor for recovery or even arrest. Gradual or intermittent progression of lesions is the rule; eventually laryngeal stenosis develops, and progresses

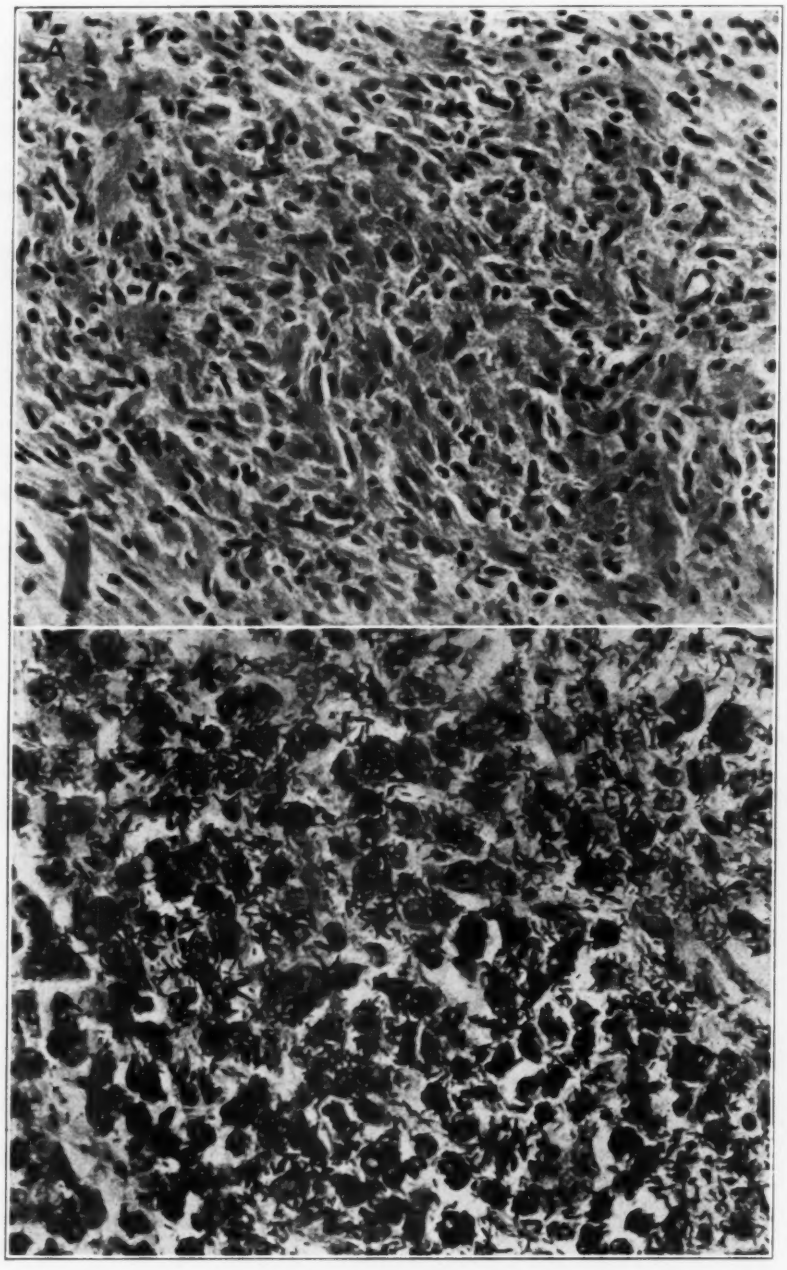

Fig. 2.—*A*, xanthoma-like infiltrate of lepromatous leprosy. Hematoxylin and eosin; × 300. *B*, granulation tissue of lepromatous leprosy showing abundance of leprosy bacilli. Fite's fuchsin-formaldehyde; × 600.

lesions more extensive, than before. Such reactions may be precipitated by the menarche, an individual mensis, pregnancy or an intercurrent illness. They may also occur without any apparent precipitating factor.

to such a point that tracheotomy is required; tuberculosis frequently develops; and eventually the patient, still leprous, succumbs to tuberculosis (in nearly half the cases) or renal disease (in about one sixth of cases) or some other

condition. In a small proportion of cases, apparently without any constant relation to treatment, the lesions slowly subside and eventually become poor or even lacking in acid-fast bacilli, leaving only the residual neurologic changes; such a patient is sometimes said to have a "secondary neural" case. This process, which is tantamount to recovery, is rare even in cases of long standing and exceedingly rare in earlier cases. Its occurrence casts some doubt on the validity of the original classification of the case, as will be brought out under the heading of the "Tuberculoid Reaction." Hopkins and Faget's figures [5] are eloquent in this regard. Of 537 cases of lepromatous leprosy in their series, only 28 patients—5 per cent—could be listed as "discharged, disease arrested, not (yet) readmitted." Thirty-one per cent had died.

The disposition of patients with leprosy of the lepromatous type is always the same: institutionalization. These patients are like patients with "open" cases of tuberculosis from the standpoint of public health. They are the "infectious" cases of leprosy. The word is enclosed in quotation marks because the infectiousness of leprosy, even in this form, is slight, at least for most adults. Marital transmission of the disease, for example, is rare; Norman Sloan, Physician in Charge of Kalaupapa Settlement on the Island of Molokai in Hawaii, says that not one of the nearly 400 patients now under his care is suspected of having acquired the disease from a spouse; and the recent report from Carville by Hopkins and Faget [5] listed only 2 instances out of over 700 cases in which evidence of leprosy in a patient had developed following marriage to a leprous person. It is believed, however, that children are much more susceptible than adults; and in any case, in the light or rather the darkness of the present state of knowledge regarding the transmission of the disease, one cannot do otherwise than isolate, in leprosaria, all patients known to have lepromatous leprosy.

"NEURAL" LEPROSY

"Neural" leprosy is that form of the disease which was once known as *leuce Graecorum*. Bateman [1] cites Celsus, Aetius, Aeginet and Actuarius as clearly describing a pale color and cutaneous anesthesia as the leading symptoms of a disorder under this name. He also cites Avicenna and Alsaharavius to the effect that *leuce* "possessed an affinity with" the *elephantiasis* of the Greeks. More recent synonyms for this form of leprosy are "macular," "anesthetic" or "maculoanesthetic" leprosy. The term "neural" has been official since 1931, when it was adopted at the Leonard Wood Memorial Conference on leprosy, in Manila.[7] It was officially redefined in March 1938 at the First International Congress on Leprosy, in Cairo, as follows:

> *Neural (N) type.*—All cases of the "benign" form of leprosy, with disturbances of polyneuritic nature (i. e., alterations of peripheral sensation, trophic disturbances, atrophies and paralyses, and their sequelae), or *macules of nonlepromatous nature* [italics mine] (i. e., leprides, usually with localized sensory disturbances), or both. These cases give evidence of relative resistance to the infection, are of relatively good prognosis as regards life, although mutilation may take place, and usually react positively to leprolin *(sic)*.[8] Bacteriologically the skin lesions are typically but not invariably found negative by standard methods of examination, though the nasal mucosa may be found positive. Many of these lesions are histologically of tuberculoid nature.

"Neural" leprosy is therefore by no means synonymous with "nerve" leprosy, most modern textbooks to the contrary notwithstanding. The word is enclosed in quotation marks to remind the reader that this is the case. "Neural" leprosy involves both skin and nerves, as well as lymph nodes and perhaps testicles (Mitsuda [2]). The term "neural" is not only inapt, but an important source of serious confusion. Pardo-Castello [10] and Tilden and I [11] have suggested its abandonment and the adoption of "tuberculoid" in its place. The additional "simple inflammatory" category suggested by Pardo-Castello seems necessary for certain *lesions*, but I am not convinced that it is necessary for any *cases*, of the disease. It seems probable that a sufficiently thorough search would reveal tuberculoid histologic changes somewhere in virtually every case of this so-called "neural" type of leprosy.

"Neural" leprosy is characterized, then, by "disturbances of polyneuritic nature." So, however, is lepromatous leprosy. This feature is valueless in distinguishing between the two forms of the disease, except in one single respect: the distribution of the sensory disturbances in "neural" leprosy is likely to correspond at least in part to the extent of the cutaneous lesions

7. Wade, H. W.: A Proposed Revision of the Memorial Conference Classification of Leprosy, Am. J. Trop. Med. **17**:773 (Nov.) 1937.

8. "Lepromin" is meant. This was an error in terminology which was subsequently explained and corrected.

9. First International Congress on Leprosy, Internat. J. Leprosy **6**:377 (July-Sept.) 1938.

10. Pardo-Castello, V., and Tiant, F. R.: Leprosy, J. A. M. A. **121**:1264 (April 17) 1943.

11. Tilden, I. L., and Arnold, H. L., Jr.: The Two Kinds of Leprosy: Lepromatous and Tuberculoid, Proc. Staff Meet. Clin., Honolulu **10**:91 (Sept.) 1944. Arnold, H. L., Jr., and Tilden, I. L.: The Classification and Nomenclature of Leprosy, with Suggestions for the Simplification of Both, Ann. Int. Med. **23**:65 (July) 1945.

themselves. This is, as has already been stated, seldom true of lepromatous lesions. To put it more explicitly, a hypopigmented macule—a lesion characteristic of "neural" leprosy—is often found to be anhidrotic and anesthetic to heat or cold or both. Almost invariably, it also presents loss of the "axon reflex": a dermographic wheal, or a histamine wheal, will manifest no surrounding erythema (flare) within the hypopigmented area. The same statements are true of the elevated, granulomatous, frequently annular plaques which also characterize this form of leprosy.

Secondly, "neural" leprosy is characterized by "macules of nonlepromatous nature (i. e., leprides . . .)." They are dealing here with "macules" in the leprologic sense, not the dermatologic sense. In this usage a "macule" or lepride is a circumscribed lesion, usually hypopigmented (fig. 3), not infrequently erythematous and infiltrated and elevated, and when elevated often annular in configuration (fig. 4).

Fig. 3 (case 2).—Hypopigmented, thermally anesthetic "simple macules" of "neural" leprosy.

Thirdly, these lesions are nonlepromatous: i. e., they are typically poor or lacking in acid-fast bacilli "by standard methods of examination." This refers to the search for bacilli in thick smears of serum obtained from the cutaneous lesions by Wade's "scraped incision" method. The point of a scalpel or the corner of a safety razor blade is used to make a linear incision perpendicular to the surface of the skin and about 3 mm. deep, and then the blade is rotated so that its edge scrapes one surface of this incision, removing a droplet of serum and a few cells. This is deposited (not smeared) on a slide, allowed to dry, fixed, stained and examined. This procedure almost invariably serves to demonstrate abundant bacilli in lepromatous cases, but usually shows very few, or more often no, bacilli in "neural" cases. An important exception to this rule is occasionally encountered: the so-called tuberculoid reaction. This is characterized clinically by little more than an apparent aggravation of existing lesions, some-

Fig. 4.—Typical elevated annular tuberculoid "macule" of "neural" leprosy. The central portion, characteristically, was anesthetic. Biopsy scar in upper part of lesion.

times acute enough to produce superficial ulceration of them. There is typically little or no fever, and erythema multiforme does not occur. Bacilli, however, may be present in the lesions over a period of weeks or months, and it is possible for patients to be erroneously classified as lepromatous during this bacteriologically positive phase.

The fourth characteristic of "neural" leprosy is that "many of these lesions are histologically of tuberculoid type." It has been shown repeatedly by Wade,[12] Lowe,[13] and many others,[14] and

12. Wade, H. W., and Rodriguez, J. N.: Borderline Tuberculoid Leprosy, Internat. J. Leprosy **8**:307 (July-Sept.) 1940; The Skin Lesions of Neural Leprosy: II. Observations in Cebu, ibid. **5**:1 (Jan.-March) 1937. Wade, H. W., and Fraser, N. D.: The Skin Lesions of Neural Leprosy: III. Observations in China, ibid. **5**:285 (July-Sept.) 1937. Wade, H. W.; Cochrane, R. G., and Raj, M. P.: The Skin Lesions of Neural Leprosy: IV. Observations in Madras, South India, ibid. **5**:437 (Oct.-Dec.) 1937. Wade, H. W.; de Simon, D. S., and Fernando, A. C.: The Skin Lesions of Neural Leprosy: V. Observations in Ceylon, ibid. **6**:199 (April-June) 1938.

(Footnotes continued on next page)

has been found to be true in Hawaii, that epithelioid cell tubercles with lymphocytic infiltration are regularly found in cases of "neural" leprosy when the lesions show any perceptible infiltration, and sometimes even when they do not. These tubercles are rather sharply circumscribed, and are generally less closely packed together than is the case in Besnier-Boeck-Schaumann's sarcoidosis, which they otherwise closely simulate (fig. 5). They rarely show any trace of necrosis when they occur in the skin, but in nerve trunks caseation necrosis occurs frequently. Acid-fast bacilli may be found in them, in small numbers and after prolonged search, almost invariably, even in cases in which repeated examinations of material obtained by the scraped incision method have failed to demonstrate the organism (fig. 6).

The skin of patients with "neural" leprosy regularly reacts positively to injected lepromin. This positive reaction does not indicate the presence of leprosy; it is also found frequently in adults, and less often in children, who do not have the disease. It is believed that such a reaction is seen more frequently in countries where leprosy is endemic. The positive reaction consists, as has been stated, of an infiltrated red papule which takes two to three weeks to develop, and may ulcerate. Histologically, the mature reaction closely resembles the picture of reacting tuberculoid leprosy, foci of epithelioid cells occurring among and around the myriads of injected (dead) Myco. leprae.

Positive reactions to serologic tests of the blood for syphilis probably occur in "neural" leprosy in the absence of syphilis, but the evi-

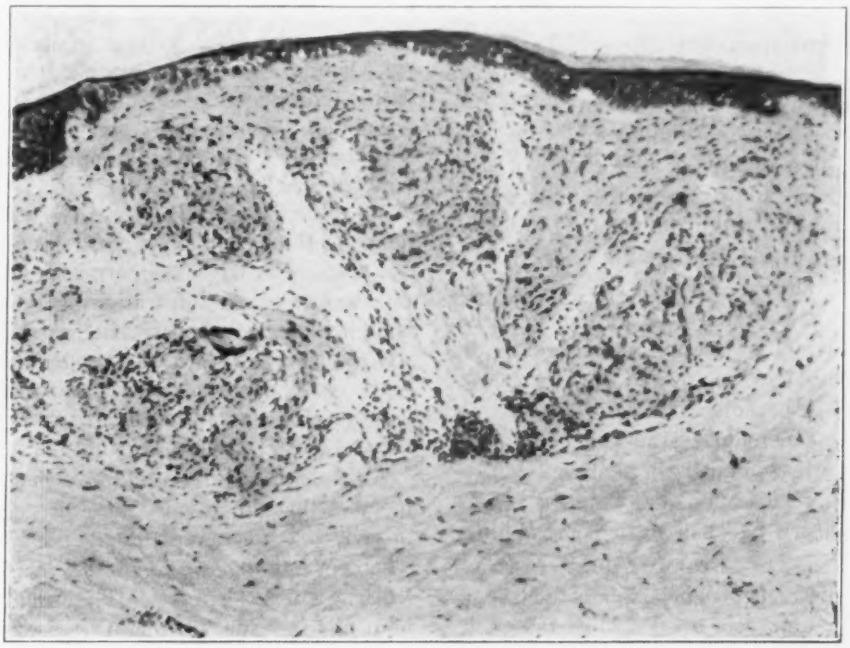

Fig. 5.—Four typical noncaseating epithelioid-cell tubercles of "neural" leprosy of "tuberculoid" subtype. Giant cell in the lower left hand tubercle. The superficial similarity to sarcoidosis is apparent. Hematoxylin and eosin; × 130.

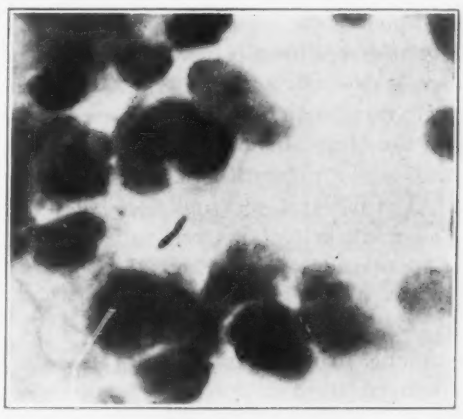

Fig. 6 (case 2).—Solitary Mycobacterium leprae in one of the macules shown in figure 3. Fite's fuchsin-formaldehyde; × 1,800.

13. Lowe, J.: A Study of Macules in Nerve Leprosy with Particular Reference to the "Tuberculoid" Macule, Internat. J. Leprosy **5**:181 (April-June) 1937.

14. Ermakova, N.: The Histopathology of Simple Leprids, Internat. J. Leprosy **7**:495 (Oct.-Dec.) 1939. Stein, A. A.: Tuberculoid Changes in Leprosy, ibid. **8**:41 (Jan.-March) 1940. Saunders, G. M., and Giffen, H. K.: The Skin Lesions of Neural Leprosy in the Virgin Islands of the United States, ibid. **10**:38 (Jan.-March) 1942.

dence is less conclusive than is the case with lepromatous leprosy. Hopkins and Faget [5] found 11 per cent positive Kolmer Wassermann reactions in 175 "neural" cases, and 13 per cent positive Kahn reactions. Badger,[6] interestingly, found no difference in this regard between cases with cutaneous and those with neural sites of involvement.

The prognosis of "neural" leprosy is good for arrest and even fairly good for recovery. It is not generally believed that treatment, except perhaps for the good effect of rest and improved diet implicit in a hospital regimen, has any observable effect in this regard. Improvement, like aggravation of lesions, seems to be spontaneous. It is believed to occur as a result of the patient's immune reaction to the presence of the bacillus, as manifested in the positive reaction to the lepromin test. It is by no means unusual to see a patient with a few tuberculoid "macules" begin to improve within a year or so of their initial appearance, and recover almost completely, except perhaps for residual flushing or dyspigmentation of the area, within another year. The associated anesthesia may disappear as well, though more advanced neurologic changes, such as muscular atrophy or contractures, seldom disappear entirely. In Hopkins and Faget's series of 186 "neural" cases (of which 31 were classified separately as tuberculoid), 56 per cent of the patients were listed as discharged and not yet readmitted in relapse, and only 8 of a total of 110 so discharged had had to be so readmitted.

The disposition of cases of "neural" leprosy is not always the same. They do not all require institutionalization. It is probable that some official body should assume the responsibility for deciding that hospitalization is not required in any given case. It is the practice in Hawaii to hospitalize all patients with acid-fast bacilli demonstrated by the scraped incision method, and also to hospitalize most patients in whom the disease seems clinically active: i. e., those who have elevated, erythematous, infiltrated or ulcerated lesions. The latter are hospitalized not so much as menaces to the public health, as for their own good: It is felt that rest and adequately supervised diet are helpful in accelerating the onset of the spontaneous arrest.

DIFFERENTIAL DIAGNOSIS

Assuming that the diagnosis of leprosy has been arrived at or at least strongly suspected, how is the distinction to be made, in office or clinic practice, between lepromatous and "neural" types?

Dermatologic Differentiation.—The distinction may often be made with reasonable assurance on the basis of inspection alone. This does not mean inspection with a view to deciding whether leprous involvement is primarily neurologic or primarily cutaneous; such a distinction is utterly valueless. Notwithstanding this fact, it has been widely employed, often by men who should and do know better. It must be kept clearly in mind at all times that leprosy of nerves, like leprosy of skin, may be either lepromatous or "neural" in type; it is not the *tissue* that has the disease, but the *entire patient,* that must be considered.

The oldest clinical evidence is perhaps the best clinical evidence: Has the patient hypopigmented macules, or has he not? Hypopigmented macules are frequently present in "neural" leprosy, and they are seldom present in lepromatous cases. If this test fails, look for an annular configuration of the lesions. The lepromas of lepromatous leprosy are seldom annular, while the tuberculoid "macules" of "neural" leprosy are frequently so. Positive evidence of the lepromatous nature of a lesion does not rest on nearly as secure ground. Striking diffuse or nodular infiltration of the ears or face is highly suggestive of lepromatous leprosy. It is well, however, to make only a tentative decision on the basis of inspection of the patient; in making this differentiation experience is indeed fallacious and judgment difficult.

Neurologic Differentiation.—One must remember that the absence, or presence, or extent, of evidence of nerve damage has no bearing whatever on the differentiation of lepromatous from "neural" leprosy. The important point here is to decide whether the visible cutaneous lesions tend to coincide in extent with the demonstrable anhidrosis, or anesthesia, or loss of the flare about the histamine wheal. If this is the case—if nerve damage can be demonstrated just within the border of the hypopigmented or annular lesion—it is highly probable that the case is a "neural" one. If this is not the case, the evidence is slightly, though only very slightly, in favor of the lepromatous form of the disease.

Bacteriologic Differentiation.—Bacteriologic examination, in the majority of cases, will make the distinction reasonably secure if bacilli are scanty or absent. Such a finding is strongly suggestive of the "neural" type of the disease. If bacilli are fairly numerous, it means that the patient has either lepromatous leprosy or (less probably) "neural" leprosy in a transitory tuberculoid reaction. Only a series of examinations over weeks or months will permit evaluation of such a case on bacteriologic grounds, and some-

times this is the only way of arriving at the differentiation. This examination is readily made in the office by Wade's scraped incision method, as already described. A proper preparation should contain few red blood cells, and should show at least one or two lymphocytes or histiocytes in almost every oil immersion field. The usual Ziehl-Neelsen stain is perfectly satisfactory if decolorization is not overdone.

A special word of warning should be inserted here. Nasal scrapings or smears are worthless at best, and misleading at worst, in the diagnosis of leprosy or the differential diagnosis of the two types of the disease. It is perfectly true that lepromatous lesions of the nasal mucous membrane are fairly common, and that Myco. leprae can be found with ease in scrapings from such lesions. But it is also true that acid-fast diphtheroid bacilli morphologically indistinguishable from Myco. leprae may be found in either the normal or the leprous nasal mucous membrane, and conversely, that a leprous patient may fail to show acid-fast bacilli of any sort in nasal scrapings. Eskey,[15] at Kalihi Hospital in Honolulu, was able to cultivate acid-fast bacilli repeatedly from nasal scrapings taken from leprous patients. The two conclusions are inescapable: (1) The presence of acid-fast bacilli in smears of nasal scrapings does not mean that the patient has leprosy, and (2) the absence of such bacilli does not mean the absence of leprosy. Controlling the smears with cultures will not help, because negative cultures would be inconclusive and positive cultures would not exclude the possibility that Myco. leprae was also present. The examination of nasal smears or scrapings has, therefore, no place in the diagnosis of leprosy or in the differentiation of the two types.

Histologic Differentiation.—The fourth step in evaluation when leprosy is suspected is biopsy. This should be made in every case. In the bacteriologically positive cases it is needed in order to distinguish, if possible, between lepromatous leprosy and reacting tuberculoid leprosy; in the bacteriologically negative cases it is desirable in order to establish the presence or absence of tuberculoid histologic changes, and it is useful in order to furnish (as it usually will) bacteriologic evidence that the lesion is actually leprous. In my experience histologic examination of sections stained by Fite's fuchsin-formaldehyde method has repeatedly served to demonstrate occasional acid-fast bacilli in lesions in which no bacilli could be found by the scraped incision procedure, and in which—in some cases—the histologic changes were nonspecific.

15. Eskey, C. R.: Personal communication to the author.

Biologic Differentiation.—These four procedures will serve to establish the differential diagnosis in most cases. In the event that doubt still exists, however, a lepromin test may be performed. In my limited experience with this test, the results have not been entirely satisfactory, possibly for technical reasons; but there can be no doubt that in general it will give a strongly positive reaction in the great majority of "neural" cases and a negative reaction in virtually all lepromatous cases. In a nonleprous person, of course, either response may be obtained. It has two major drawbacks: The material for performing it is not commercially available, and the test requires from two to four weeks for evaluation.

REPORT OF CASES

CASE 1.—A Hawaiian girl aged 13 was referred to the Clinic of the Board of Hospitals and Settlement as suspected of having leprosy because of a deep red, sharply outlined, palm-sized macule on the right forearm and the finding of acid-fast bacilli in nasal scrapings. Examination disclosed no other lesions than the one mentioned, which had the appearance of a port wine hemangioma and was said to have been present since infancy. A thorough neurologic examination disclosed no palpable nerve trunks except the ulnar nerves, which were equal and normal in size; there was no evidence of muscular weakness, atrophy or contractures; and there was no anesthesia to heat or cold anywhere on the cutaneous surface. The nasal scrapings were repeated as a courtesy to the referring physician, and no acid-fast bacilli were found in them. The diagnosis was port wine hemangioma with no evidence of leprosy. The patient was officially certified as not leprous.

Comment.—This case provides a classic example of the inadvisability of performing nasal scrapings on patients suspected of having leprosy. The "positive" finding here was the only feature of the case that even seemed to justify the suspicion of leprosy. The complete absence of thermal anesthesia in a patient whose only cutaneous lesion was of many years' standing excludes the possibility of leprosy with reasonable certainty.

CASE 2.—A part-Hawaiian woman aged 23, a housewife, was referred to the Clinic of the Board of Hospitals and Settlement as suspected of having leprosy because of anesthesia of the left foot. A biopsy had been made from the anesthetic region, and had been reported as showing only minimal, banal, perivascular inflammatory infiltration, without acid-fast bacilli.

Examination disclosed a healthy-looking young woman who presented no lesions of the skin except half a dozen sharply outlined hypopigmented macules, without erythema or infiltration, on the forearms (fig. 3). Most of the macules were anesthetic to heat and cold, though not to light touch. The left foot, from the ankle joint distally, was anesthetic to heat and cold, light touch and pinprick. No abnormal nerve trunks were noted in the neck or arms, but the left posterior tibial and sural nerves

were thickened and tender from the point where they passed beneath the malleoli to a point several centimeters distally. No acid-fast bacilli were found in fluid obtained from scraped incisions in the anesthetic portion of the foot and in two of the macules.

Biopsy from the border of one of the macules showed only moderate perivascular lymphocytic and histiocytic infiltration, but acid-fast stains disclosed half a dozen widely scattered individual acid-fast bacilli (fig. 6). A routine nasal scraping disclosed abundant acid-fast bacilli morphologically indistinguishable from Myco. leprae. The nasal scrapings were repeated forty-eight hours later on each side of the nasal septum, and no acid-fast bacilli could be found in either smear.

The diagnosis was leprosy, "neural" type, subtypes simple macular and anesthetic, minimal degree (Ns 1, Na 1). The patient was officially certified as leprous and granted immediate temporary release (parole) status, to report monthly for observation.

Comment.—This case well exemplifies the futility of using nasal scrapings as a means of distinguishing between lepromatous and "neural" leprosy. It seems highly improbable that a bacteriologically positive leprous lesion of the nasal mucous membrane would have healed or become bacteriologically negative within forty-eight hours. If the bacilli found in the first smear had been M. leprae, they should still have been readily demonstrable two days later. The most likely explanation seems to be that they were (like the organisms in case 1) nonpathogenic diphtheroid bacilli, only temporarily present. Confusion would have been avoided and no advantage lost if the nasal scrapings had not been performed.

Attention is also invited to the importance of biopsy and acid-fast stains as a means of demonstrating rare bacilli even in relatively early cutaneous lesions of "neural" leprosy.

CASE 3.—A part-Hawaiian girl aged 19 was referred to my office because of a numb area on her right calf, present for about four months. Examination disclosed no visible, and no readily palpable, abnormality. Repeated deep palpation at right angles to the border of the anesthetic area revealed just a suspicion of infiltration in that region. A deep biopsy showed replacement of nerve trunks in the hypoderm by characteristic epithelioid cell tubercles. Prolonged search of several sections finally revealed rare acid-fast bacilli in a few of these tubercles (fig. 7). The diagnosis was leprosy, "neural" type, subtypes anesthetic and tuberculoid, minimal degree (Na 1, Nt 1). Because of the absence of cutaneous lesions, the patient was not officially certified at this time, but merely kept under unofficial observation.

Seven months later, the anesthetic area underwent a typical tuberculoid reaction, with the development of a reddened, elevated, infiltrated tuberculoid annule surrounding it, and moderate spread. The patient was officially certified as leprous at this time, and was granted immediate temporary release, with instructions to report monthly for observation. In the ensuing year the lesion slowly subsided and the area of anesthesia diminished, so that at present the patient shows only faint pinkness and scaliness along the border of the original palm-sized area of anesthesia.

Comment.—This case is of interest primarily because it is unusual to see tuberculoid leprosy of the skin (or more exactly, of the smaller branches of cutaneous nerves) without any visible lesion. The case also well illustrates the great diagnostic value of biopsy even with scanty clinical evidence of abnormalities.

CASE 4.—A Japanese man aged 26 was referred to the Clinic of the Board of Hospitals and Settlement as suspected of having leprosy. Examination disclosed a young man with total alopecia of brows and lashes; left facial weakness, more evident about the eye than in the lower portion of the face; weakness, atrophy and moderate contracture of the left hand and forearm; and tactile anesthesia of both legs up to about the knees, of the entire left arm and of portions of the face. This process was said to have begun six years before with diffuse swelling of the face, diagnosed as nephritis by the family physician; shortly afterward, the patient recognized it as leprosy and thereafter avoided doctors. In recent months, some cutaneous lesions had appeared: There were dull redness and thickening of the helixes of both ears; sharply elevated, dull red, rubbery firm nodules were present on both elbows; and there was a faint pink eruption of small papules on the trunk, especially anteriorly. Bacteriologic examination of serum obtained from lesions on the ear and chest revealed abundant acid-fast bacilli in clumps and globi. Biopsy was not done. A lepromin test, a few weeks later, elicited only faint brown pigmentation in an area 3 mm. in diameter at the end of three weeks, and was interpreted as negative. The diagnosis was leprosy, lepromatous, moderately advanced (L 2). The patient was officially certified and committed to Kalihi Hospital for isolation and observation.

Comment.—The value of this case lies chiefly in its clear demonstration of the uselessness of attempting to differentiate lepromatous from "neural" leprosy by an evaluation of the relative degrees of involvement of the nerves and of the cutaneous tissue. Here is a patient with neurologic changes—alopecia, anesthesia, muscular weakness, atrophy and contracture—of moderately advanced degree, and only slight cutaneous changes, who nevertheless, as shown by bacteriologic examination, the negative lepromin test and his subsequent steady downhill course, has not the "neural" but the lepromatous form of the disease.

This is the type of case that would be classified in some clinics as "mixed" leprosy (L 2, N 2), because the neurologic involvement is moderately conspicuous. The utilization of this term to designate a separate type of the disease, besides being contrary to the explicitly expressed intention of the Cairo Congress,[9] serves only to confuse the issue, because it so clearly implies a mixture of the two types of the disease instead of, as is actually the case, a mixture of the two

major sites of involvement. Moreover, it tends to divert attention from the important fact that virtually every case of lepromatous leprosy has at least some degree of involvement of nerves as well as of skin. The term "mixed" leprosy should be abandoned altogether.

neous lesion. He presented a profuse eruption of irregularly oval, sharply outlined, hypopigmented macules scattered over the trunk; several of these on the lower part of the back and buttocks were surrounded by an elevated, reddened, infiltrated annulus varying from 1 to 3 cm. in width. All of the larger macules and a few of the smaller ones presented thermal anesthesia; none

Fig. 7 (case 3).—*A*, replacement of nerve twigs in the hypoderm by epithelioid cell tubercles. Hematoxylin and eosin; × 40. *B*, one of the tubercles from *A*. Hematoxylin and eosin; × 300. *C*, solitary Mycobacterium leprae in one of the tubercles. Fite's fuchsin-formaldehyde; × 1,800.

Case 5.—A Portuguese man aged 21 was referred to the Clinic of the Board of Hospitals and Settlement as suspected of having leprosy because of a hypopigmented macular eruption of four months' duration and the finding of acid-fast bacilli in serum obtained from a cuta-

was anesthetic to touch, nor was tactile anesthesia demonstrable anywhere on his skin. There was minimal weakness of the lower part of the left side of the face and slight interosseous atrophy in the left hand. Both hands were cyanotic when dependent, and slightly

swollen. The anterior divisions of both great auricular nerves were visible and easily palpable, and the left was nearly twice the diameter of the right. The right ulnar nerve was almost twice as thick as the left, and was rounded, firm and cordlike; the left seemed thicker than normal.

Smears of serum obtained from an infiltrated annulus on the buttock revealed only 2 acid-fast bacilli after prolonged search. Biopsy from the same lesion showed sharply outlined foci of granulomatous infiltration scattered throughout the corium and hypoderm; these were composed largely of round and spindle-shaped cells with foamy cytoplasm, and most of the foci contained from a few to 40 or 50 acid-fast bacilli. The distribution of the infiltrate was suggestive of tuberculoid leprosy, but its character was more in keeping with lepromatous leprosy. A lepromin test was made, and at the end of three weeks resulted in the formation of a brownish, slightly scaly papule 2 mm. in diameter, barely elevated above the surface. The test was interpreted as negative. The diagnosis was leprosy, type indeterminate. The patient was officially certified and committed to Kalihi Hospital for observation.

Comment.—This case presents one clinical feature of special interest and significance: there was readily demonstrable and extensive thermal anesthesia, but no demonstrable tactile anesthesia. When anesthesia to light touch can be demonstrated, leprosy may well be suspected; but when it cannot be demonstrated, thermal anesthesia should always be looked for before concluding that the sensory examination is "negative." It is decidedly commonplace, some texts to the contrary notwithstanding, to see this complete dissociation of thermal and tactile sensation.

The classification of this case poses a puzzling problem. Clinically, because of the hypopigmented and anesthetic macules and the annular lesions, it should be classified as a "neural" case, of all three subtypes—simple macular, anesthetic and tuberculoid (Na 1, Ns 1, Nt 1). Histologically it seems lepromatous, though perhaps the histologic structure could be explained on the basis of tuberculoid leprosy in a bacteriologically positive reaction. Biologically—by the lepromin test—the case also seems to be of the lepromatous type. A period of observation seems necessary before arriving at a final decision.

SUMMARY

Lepromatous leprosy is characterized by granulomatous lesions of the skin, nerves, lymph nodes and viscera; abundant bacilli; variable neurologic changes; a negative reaction to the lepromin test, and a progressive downhill course.

"Neural" leprosy is characterized by hypopigmented cutaneous lesions and sarcoid-like lesions of the skin, nerves and lymph nodes; scanty bacilli (except during reactions); variable neurologic changes; a positive reaction to the lepromin test; and a tendency to spontaneous arrest and healing.

These forms may usually be distinguished in practice by attention to the clinical appearance of lesions, by comparison of the distribution of sensory changes with that of changes in the skin, by search for bacilli in tissue fluid, by biopsy and by the lepromin test.

The distinction should always be made, when possible, because it permits a prognosis to be made, it guides the physician in his disposition of the case, it makes possible the evaluation of treatment, and—if it is favorable—it permits the physician to soften the blow when he informs the patient of the nature of the illness.

Dr. Irvin L. Tilden, of the Department of Pathology of The Clinic, Honolulu, made the histologic preparations, the clinical photographs and the photomicrographs and assisted in the preparation of the portions of the paper dealing with histopathology.

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SANDALS, AND HYGIENE AND INFECTIONS OF THE FEET

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The high incidence of cutaneous diseases of the feet due to infection and hyperhidrosis among military personnel in tropical and summer temperate climates greatly interferes with the efficient performance of military functions. The extent and severity of such infection are not generally realized. Moreover, the problem in the tropics is not peculiar to the army, and return of infected personnel may bring it into sharp focus in this country. Various estimates give the percentage of Army and Navy personnel free from clinical evidence of infection of the feet at only 20 per cent; estimates for civilian industrial populations show only a slightly better situation. Callaway [1] has stated that "no effective fungicide is yet available which does not have certain disadvantages . . . most prescribed remedies depend not on their fungicidal action but on keratolytic action." Hopkins [1] pointed out that "almost any agent that is fungistatic and not too irritating to the skin shows some curative effect." The great number of different treatments that have been proposed is in itself evidence that a specific treatment is not at hand.

An examination of dispensary records in the Army Air Forces Proving Ground Command revealed that 30 per cent of the outpatients for the months from May through October came because of infections of the feet. A similar or more serious situation is common in other commands in hot, humid climates. On the assumption that aeration was essential to hygiene of the feet, a preliminary trial with twenty pairs of open-toed sandals for everyday wear was conducted at Eglin Field. After reviewing the favorable effects on hygiene of the feet which this preliminary test showed, the Air Surgeon requested that the Army Air Forces Proving Ground Command ascertain experimentally the value of sandals in reducing infections of the feet. A controlled test with over 2,000 men was conducted for a two month period. The aid and advice of the Surgeon, Colonel J. A. Schindler, and the interest and cooperation of the entire Command made it possible to carry the test to conclusive results.

Fig. 1.—*A*, sandals were commonly worn without socks. *B*, sandals were constructed with leather sole and upper, and rubber heel; closure was effected by a single leather thong and metal buckle.

Sandals of the type shown in figure 1 were issued during the week of May 15, 1944 to 1,200 men after allocation to various components of the Command; different groups were examined on successive days of that week. In some

From the Physiological Projects Section, Proof Division, Army Air Forces Proving Ground Command.

1. Personal communication to the authors.

groups sandals were issued to every man examined, in some the men were examined but no sandals were issued, while in the remaining groups every other man received sandals. These procedures were adopted to make the distribution statistically significant.

Medical examiners classified the clinical state of infection of the feet into one of five classes,[2] from (I) negative to (V) very severe. Of 2,100 men examined during the week of May 15 (1,200 experimental, 900 control), only 19 per cent showed no visible signs of infection and 23 per cent of the men (in classes IV and V) had infections severe enough to be of medical concern. Reexaminations similar to the initial examination were held at the end of the first and second months. During this time, with a few exceptions, the men who had been issued sandals wore them to the exclusion of other types of footgear; a large number of the men wore sandals without socks. No type of treatment was given to either control or experimental groups during the period of the test.

A comparison of the incidence of infection of the feet at the beginning of the test and at the end of the second month, at which time the test was terminated, is presented in table 1 and figure 2. The figures show that the condition of wearers of sandals improved greatly while that of the control group deteriorated rapidly as the

TABLE 1.—*Incidence of Infection of Feet at Beginning of Test and at End of Second Month*

Severity Class	Initial Examination		Final Examination			
			Sandal Group		Nonsandal Group	
	No. of Men	Per Cent of Total	No. of Men	Per Cent of Total	No. of Men	Per Cent of Total
I (negative)....	397	19	373	65	120	22
II (mild).....	628	29	134	23.5	121	22
III (moderate)...	605	29	45	8	154	28
IV (severe).....	283	13.5	16	3	114	21
V (very severe)..	207	9.5	2	0.5	40	7

summer heat and humidity increased. Only 3.5 per cent of those who wore sandals were seriously affected at the end of the two month period, and with this group the disease had practically ceased to be a problem of medical concern; among the group wearing shoes 28 per cent were in a serious condition.

Colored photographs were taken of the feet of about 75 men with an initially severe infection (class IV or V). Subsequent pictures in color were taken of the same men at each of the two monthly reexaminations. Subjects were photographed in the group wearing sandals or in the control group.

Questionnaires were given to all men at the initial examination and to those who wore

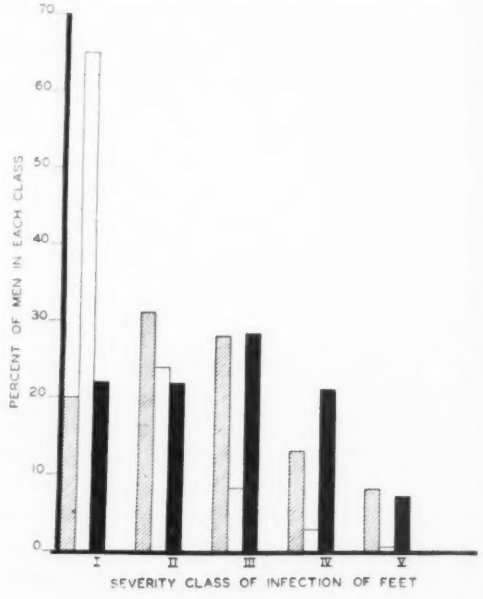

Fig. 2.—Summary of infections of feet at beginning and end of sandal test. The cross-hatched columns indicate results of initial examination; the white columns, results in group wearing sandals, and black columns, results in group not wearing sandals. The class of severity of infection is indicated thus: *I*, normal; *II*, mild; *III*, moderate; *IV*, severe, and *V*, very severe.

sandals at the first reexamination. From the answers it was learned that the sandals were extremely popular with the men; 88 per cent of the wearers liked them and 84 per cent preferred sandals to low quarter shoes for wear during the hot months, while 87 per cent preferred them to service shoes. While on the first questionnaire 99 per cent of the men said their feet perspired noticeably while wearing shoes during the hot months, 87 per cent of those who wore sandals said at the end of one month that their feet did not get sweaty.

A method was selected to express how much better or how much worse a man became during

2. Classes were defined as follows: (I) Negative. (II) Mild: mild or slight scaling, redness; closed, initial, or slight fissures. (III) Moderate: moderate scaling, redness; mild to moderate fissures; slight sodden patches, mild tissue changes. (IV) Severe: severe scaling, sodden patches, fissures, tissue changes. (V) Very severe: marked eczematoid condition, severely aggravated condition, very severe sodden patches and fissures, extreme vesiculation, marked tissue changes.

3. Two comparison sets appeared in color in Nickerson, W. J.; Irving, L., and Mehmert, H. E.: Effect of Wearing Sandals in Reducing Foot Infections, Air Surgeons' Bull. **2**:120-121, 1945.

the course of the test. One man improving one class constitutes one positive unit; one man deteriorating one class constitutes one negative unit. On the basis of the initial and final examinations, the overall figures are given in table 2 (it was possible to get back 1,119 of the men originally examined for the second reexamination):

TABLE 2.—*Severity Class of Changes During Test at End of Second Month*

Group with Sandals	Control
570 worse 4% (—32 units)	217/549 worse 40% (—307 units)
570 same 29%	185/549 same 34%
570 better 67% (+715 units)	147/549 better 26% (+193 units)
683 — units / 570 men = 1.2 class improvements per man	114 — units / 549 men = 0.2 class deterioration per man

At the end of the first month of the test it was found that the group wearing sandals had improved an average of 1 class per man while the control group had deteriorated ⅕ class per man. At the end of the second month, as shown in table 2, the average change was 1.2 class improvements per man for the group wearing sandals and ⅕ class deterioration for the controls.

It is significant that many men in the group wearing sandals, who initially had serious conditions of the feet which improved while they were wearing sandals, reverted to a serious condition if and when it became necessary for them again to wear shoes routinely. In table 3 data on this point are presented for a group of 89 men

TABLE 3.—*Condition After Wearing Sandals and After Again Wearing Shoes*

First Month—Sandals
27/89 men or 30% worse (—41 units) 23/89 men or 28% no change 39/89 men or 47% improved (+65 units)
Plus 24 units / 89 men = 0.25 units per man improvement
Second Month—Wearing Shoes
55/89 men or 62% worse (—89 units) 19/89 men or 21% no change 15/89 men or 17% improved (+24 units)
Minus 65 units / 89 men = 0.73 units per man deterioration

whose sandals were no longer serviceable at the end of the first month of the test.

It is noteworthy that only 1 case of trauma, preventable by wearing service shoes, was reported while the group of 1,200 men was wearing sandals during the two month period of the test. This case was a first degree burn of a small area of one foot suffered by a welder.

It was noted during the examinations that two general categories of conditions of the feet exist; they occur among those with the more severe cases and fall into our classes III, IV or V. The first type may be called "sodden" and is characterized by extensive dead white, sodden areas at the base of toes where they may be tightly opposed; extensive and severe fissuring at the base of toes commonly accompanies this type; fungi can rarely be isolated from the lesions, but Staphylococcus aureus is frequently found. The second type of condition can be called "vesicular" and is marked by the presence of numerous small vesicles with considerable itching as an accompaniment; this irritation frequently results in severe aggravation at the site due to scratching. It was thought that the sandals might be having more effect on one of these types than on the other, so the data were analyzed with this in mind.

TABLE 4.—*Effect of Sandals on Sodden and on Vesiculative Condition of Feet*

Sodden Type—First Monthly Reexamination	
Sandal Group	Control Group
14/235 or 6% worse	46/142 or 32% worse
33/235 or 14% no change	49/142 or 35% no change
188/235 or 80% better	47/142 or 33% better
Vesiculative Type—First Monthly Reexamination	
Sandal Group	Control Group
9/127 or 7% worse	13/37 or 35% worse
26/127 or 21% no change	14/37 or 38% no change
92/127 or 72% better	10/37 or 27% better

As will be noted, there is no significant difference in the effect of wearing sandals on either type of infection—both respond equally well.

During the two month period of the test 16 men in the control group were admitted to the hospital for severe dermatitis or cellulitis of the feet; in the corresponding period only 1 man from the group wearing sandals was admitted for similar reasons. The average stay was thirteen days in the hospital for these 17 men. Thus two hundred and eight days in the hospital were chargeable to the 900 men wearing shoes while only thirteen days were used by the 1,200 men wearing sandals; a substantial economy of duty time and medical attention was effected by the use of sandals in these serious cases alone. The 16 not wearing sandals who were hospitalized were issued sandals on being discharged from the hospital; it was estimated that the men were able to leave, on an average, five days earlier than if sandals could not have been issued.

Thus it appears that by wearing sandals cutaneous diseases of the feet of the type observed can practically be removed as a cause for serious medical concern. In fact, in the experimental groups the incidence of infection of the feet was so low at the conclusion of the test as to suggest the possibility of eliminating the disease entirely from an organization if the general use of sandals as a prophylactic measure was occasionally supplemented by mild medicative treatment.

From what appears to be known, dermatophytosis seems only recently to have become the widespread problem that it is, and would seem to be one more on the growing list of "diseases of civilization."

Lewis and Hopper [4] state, "One of the factors thought to be important in predisposing toward fungus infections of the toes is the moisture normally present or due to lack of drying after a bath or other conditions." It is known from many sources that moisture, in some form, is a prerequisite for germination of fungus spores and continuance of growth of the organisms. The results of the present study seem to afford ample confirmation of the view, held by many, and reflected in the statement from Lewis and Hopper, that evaporation of moisture from perspiration is of great importance in protecting the feet from infection.

It might be profitable to think that the value of sandals lies in the fact that they prevent the accumulation of sweat, and by aeration and free movement of toes favor a good cutaneous circulation, which is one of the best barriers against infection.

For part of the week of the second reexamination two observers for the National Research Council were present at this study: Dr. J. L. Callaway, Duke University Hospital, and Dr. J. G. Hopkins, Columbia College of Physicians and Surgeons. Dr. Fred Wulsin and Lieut. Col. J. R. Scholtz gave advice and encouragement.

4. Lewis, G. M., and Hopper, M.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1939.

THE ADRENAL GLANDS IN PEMPHIGUS VULGARIS

REPORT OF SIX AUTOPSIES AND REVIEW OF THE LITERATURE

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Although the literature dealing with pemphigus is extensive, the greatest proportion relates to therapy or etiologic investigations; only a small fraction concerns itself with the pathology, pathophysiology or histochemistry of this disease. Biochemical changes were noted as far back as 1872, when Krieger [1] remarked on the absence of urinary chlorides in 1 case. In the last decade a great deal of study has been devoted to the changes in electrolyte metabolism.[2] This work, however, was of more or less academic interest until Talbott, Lever and Consolazio [3] called attention to the fact that the electrolyte pattern, particularly in cases of acute pemphigus, was almost identical with that observed in cases of acute adrenal insufficiency. The therapeutic consequences of these observations apparently mark a great step forward in the treatment of certain types of pemphigus. Goldman,[4] Goldzieher,[5] Gellis and Glass [6] and Talbott and others [7] have used adrenal cortex extracts or desoxycorticosterone acetate (with or without vitamin supplements) and have induced remissions in a significant number of cases; in some instances permanent remission seems to have been obtained. In cases in which the disease eventually became refractory to cortex extracts there has been subsequent response to the synthetic sterol.[4]

In view of the characteristic electrolyte pattern that had been observed and in view of the promising therapeutic results that had been obtained on this basis, it appeared worth while to investigate the morbid anatomy of the adrenals in patients with pemphigus vulgaris. The present communication is the report of the observations in 6 cases coming to autopsy at New York City Hospital, Welfare Island, New York.

REVIEW OF THE LITERATURE

Of the 105 autopsy reports in the literature, only a small proportion (as indicated in the table) contribute to this investigation. In 42 protocols, the adrenals are not mentioned at all. In 15 others, they are dismissed with the single word "normal." The misleading phrase "postmortem autolysis" seems to exclude an additional 8. In only 8 cases of the entire group are the adrenals described in detail; some data can be gleaned from 16 of the 37 cases in which they are inadequately described.

Two cases terminated in the patient's having Addison's disease. Tomlinson and Cameron [8] described the adrenal cortex as "almost entirely degenerated, with only occasional nests of cortical cells in the connective tissue stroma." The case of Becker [9] reported by Wells and others [10] appears to have been remarkably similar; the adrenal lesions were "typically those of Addi-

From the Laboratory of Pathology, New York City Hospital, Welfare Island, and the Department of Hospitals, New York City.

1. Krieger, K.: Ein Fall von Pemphigus Foliaceus, Memorabilien, Heilbr. **17**:531-540, 1872.

2. Cassaet, E., and Micheleau, E.: Sur deux cas de pemphigus traité par la dechloruration, Arch. gén. de méd. **1**:129-140, 1906. Prakken, J. R.: Weitere Untersuchungen über die erhöhte Ausscheidung von Chlor durch die Haut bei Pemphigus, Acta dermat.-venereol. **17**:103-111 (April) 1936.

3. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus, J. Invest. Dermat. **3**:31-68 (Feb.) 1940.

4. Goldman, A.; Markham, M. J., and Schaffer, A. I.: Clinical Report of Treatment of Case of Pemphigus with Desoxycorticosterone Acetate, J. Clin. Endocrinol. **2**:343-344 (May) 1942.

5. Goldzieher, M. A.: The Adrenal Glands in Health and Disease, Philadelphia, F. A. Davis Company, 1944, p. 680.

6. Gellis, S., and Glass, F. A.: Pemphigus: Survey of One Hundred and Seventy Patients Admitted to Bellevue Hospital Between 1911 and 1941, Arch. Dermat. & Syph. **44**:321-336 (Sept.) 1941.

7. Lever, W. F., and Talbott, J. H.: Pemphigus: A Further Report on Chemical Studies of the Blood Serum and Treatment with Adrenocortical Extract, Dihydrotachysterol or Vitamin D, New England J. Med. **231**:44-51 (July 13) 1944.

8. Tomlinson, C. C., and Cameron, O. J.: Juvenile Pemphigus: Effects of Germanin in Three Cases, Arch. Dermat. & Syph. **38**:555-568 (Oct.) 1938.

9. Becker, F. T., in discussion on Michelson, H. E.: Pemphigus Vulgaris Showing Remission After Treatment with Germanin; Dermatitis Medicamentosa, Arch. Dermat. & Syph. **36**:240 (July) 1937.

10. Wells, H. G.; Humphreys, E. M., and Work, E. G.: Significance of Increasing Frequency of Selective Cortical Necrosis of the Adrenal as Cause of Addison's Disease, J. A. M. A. **109**:490-493 (Aug. 14) 1937.

son's disease, except there was no evidence of regeneration. The entire cortical epithelium had almost disappeared leaving stroma containing only distended capillaries . . . round cells . . . and occasional groups of living cortical cells which were abnormally large."

Balbi [11] found "a state of maceration and disorganization so that many areas could not have been secretory. Other areas . . . show degenerative changes varying in extent and severity . . . and small foci of infiltration. We are dealing with a real, acute interstitial suprarenitis of nodular variety." In a second case there were a patchy depletion of lipids and a scanty zona reticularis. In 2 there were only adenomatous changes, and in 1, "advanced putrefaction." Talbott and others [3] found occasional foci of lymphocytic infiltration especially in the region of "small necrotic areas." In a second case there was infarction of the left adrenal; in a third there were "cystic changes of the medulla," and in a fourth bilateral hemorrhages and a necrotic medulla. In the last case the cortical cells were said to be "well preserved"—a conclusion which seems rather doubtful. Fivoli [12] found degeneration and loss of cortical cells in 1 case. Chiale [13] noted "initial degeneration," "initial fibrosis in the reticularis" in 7 cases—conditions dismissed as postmortem changes. Sarason [14] found what he classified as acute toxic changes in 1 case. Buschke and Langer [15] found "atrophy" in 1 case and Földvári [16] "hypoplasia" and "atrophy" in 2. Gellis and Glass [6] found a thickened, nodular cortex in 1 case. Eliassow and Sternberg [17] found advanced tuberculosis of the adrenals in a single case of pemphigus.

Description of the Adrenal Glands in the Autopsy Protocols of 105 Cases of Pemphigus

Observer	Cases Reported	Adrenals Not Mentioned	Adrenals "Normal"	"Post-mortem Autolysis"	Inadequate Description	Detailed Description
Talbott, Lever and Consolazio [3]	7	1	2	..	3	1
Gellis and Glass [6]	9	..	6	2	1	..
Balbi [11]	5	..	..	..	1	4
Wells, Humphreys and Work [10]	1	..	..	..	..	1
Buschke and Langer [15]	1	..	..	..	1	..
Buschke, A., and Ollendorff, H.: Dermat. Wchnschr. **81**:1591, 1925	1	..	..	..	1	..
Chiale [13]	10	1	2	..	7	..
Eliassow and Sternberg [17]	1	..	..	..	1	..
Fivoli [12]	23	2	..	1	19	1
Földvári [16]	37	35	..	..	2	..
Martinotti, L.: Gior. ital. di dermat. e sif. **63**:554, 1928	5	..	5	..	..	..
Sarason [14]	1	..	..	..	1	..
Tobias, H.: Am. J. Dis. Child. **48**:1084 (Nov.) 1934...	1	1	..	..	..	..
Tomlinson and Cameron [5]	1	..	..	..	..	1
Werth, J.: Arch. f. Dermat. u. Syph. **183**:483, 1942...	2	2	..	..	..	..
Total	105	42	15	3	37	8

REPORT OF CASES

CASE 1.—The patient was a 76 year old white woman. The duration of the disease was thirty-two days.

She was hospitalized because of chronic heart failure. A mild itching of the back had been noted for two weeks. Twelve days after she was admitted to the hospital palmar erythema was noted, and examination of the back revealed many large bullae. Nikolsky's sign was elicited. The bullae spread rapidly, and the patient's temperature hovered about 101 F. and rose terminally to 104.5 F.

Autopsy.—The entire skin was covered with bullous lesions, many of which had rubbed off, and others were covered by thick yellow crusts. Evidences of aortic stenosis, chronic cholecystitis and cholelithiasis, atrophic gastritis and early bronchopneumonia were found.

Adrenals: Gross examination. The glands were somewhat grayish with yellow flecks. The area of the corticomedullary junction was soft and friable.

Microscopic examination. There were small isolated islands of cortical cells clustered about the main artery some distance from the adrenal. A few ganglions and their nerve bundles were surrounded by a pronounced infiltration of lymphocytes and plasma cells. The capsules were normal. The zona glomerulosa had striking rectangular and wedge-shaped areas of necrosis (fig. 1) surrounded by a zone of congestion, and only cellular outlines remained within these areas. Otherwise, the

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17. Eliassow, A., and Sternberg, A.: Ein Fall von Pemphigus foliaceus nebst Bemerkungen über die Todesursache bei Pemphigus, Dermat. Ztschr. **42**:186-196 (Nov.) 1924.

zona glomerulosa was generally well preserved. Most of the cells were of average size, and the cytoplasm was granular and slightly basophilic. There were, however, numerous cells with scanty cytoplasm and pyknotic, intensely basophilic nuclei. Only finely granular lipid was present in the cells. There was uneven engorgement of the interglomerular capillaries. There was no stromal proliferation. Small patches of lymphocytes were visible. The zona fasciculata was disarranged by a number of small nodules whose cells were somewhat larger than those of the surrounding parenchyma. Many cords were broken by necrosis or complete disappearance of the cells, leaving collapsed, empty stroma. Occasionally only loosely scattered cells were left; even the best preserved of these were small and basophilic. The capillaries of the zona reticularis were engorged and the stroma was prominent, but there was no evidence of proliferation. There was decided fissuring. The scanty parenchyma consisted of small brown-pigmented cells with an occasional coarse lipid granule. In the medulla no changes were observed, except in the islands of cortical cells which were undergoing degeneration.

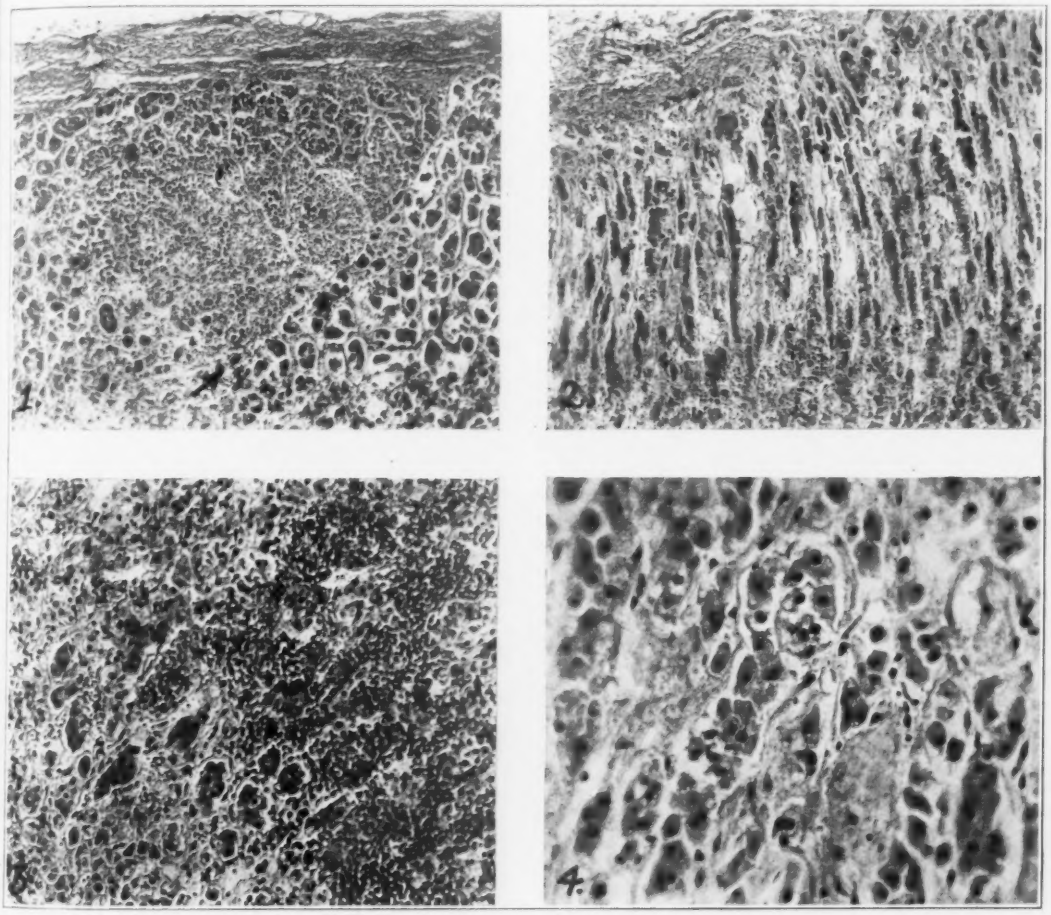

Fig. 1 (case 1).—Wedge-shaped area of disrupted necrotic cortical cells surrounded by a zone of intense congestion (arrow). Mallory's acid fuchsin stain.

Fig. 2 (case 6).—Loss of glomerular layer. Decided destruction of columns of the zona fasciculata. Hematoxylin and eosin stain.

Fig. 3 (case 2).—Intense infiltration of the zona reticularis with lymphocytes and plasma cells. Marked loss of parenchyma. Hematoxylin and eosin stain.

Fig. 4 (case 2).—Extensive destruction of the fasciculate layer. Note the absence of spongiocytes. Hema- Hematoxylin and eosin stain.

CASE 2.—The patient was a 58 year old white woman. The duration of the disease was from ten to eleven weeks.

Eight to nine weeks before the patient was admitted to the hospital a "blood blister" appeared on the leg and gradually spread over the extremity, and finally blisters became generalized. The patient slowly became drowsy, irrational and incontinent. Physical examination revealed a bullous and pustular eruption and a moderately enlarged liver. The value for nonprotein nitrogen was 121 mg. per hundred cubic centimeters, rising to 275 mg. terminally. Albuminuria was constant. Low grade fever was present throughout the twelve day hospital course.

Autopsy.—A generalized bullous, pustular and hemorrhagic eruption involved the skin, mucous membranes and conjunctivas. Evidences of pulmonary edema, early

bronchopneumonia, acute and chronic cystitis and chronic pyelonephritis were found.

Adrenals: Gross examination. The color was grayish and the consistency firm. No evidences of hemorrhages or cavitation were found.

Microscopic examination (fig. 5). Small foci of lymphocytes were observed in the pericapsular tissue. One small ganglion and the radiating nerves were surrounded by a cuff of round cells. The capsule was thin; the fibrils were hyalinized, and occasional fibroblasts were seen. The zona glomerulosa had small groups of atrophic cortical cells scattered throughout the prominent stroma, but it was well preserved in other areas. The zona fasciculata was irregularly narrowed, consisting of isolated cell groups separated by an ample stroma, in which degenerating cortical cells were still visible (fig. 4). In other areas, there was irregular, nodular proliferation of cortical cells, which were mostly small and acidophilic. No spongiocytes were found anywhere, but some of the cells contained scanty finely granular lipid. The zona reticularis was rather broad, and its cells contained golden brown pigment or showed advanced stages of disintegration. The capillaries were engorged, and a few small fissures were observed. There was intense lymphocytic infiltration, which in one area almost replaced the parenchyma (fig. 3). The medulla was interspersed with groups of acidophilic cortical cells; otherwise, it was entirely normal.

Case 3.—The patient was an 81 year old Negro. The duration of the disease was about four months.

Three to four months before admission to the hospital the patient was struck by a wooden chip, and the area involved became infected. Blisters formed around it and then spread, becoming generalized. The patient suffered severe malaise, chills and progressive weakness. Physical examination revealed signs of a recent loss of weight, a generalized eruption sparing only the face and palms, and a general lymphadenopathy. Examination of the blood showed 27 mg. of nonprotein nitrogen, 130 mg. of sugar, 80 mg. of cholesterol, 33 mg. of cholesterol esters and 406 mg. of chlorides per hundred cubic centimeters. The course was steadily downhill, and death occurred on the sixteenth hospital day.

Autopsy.—A bullous, pustular and crusted eruption involved the skin, oral mucosa and conjunctivas. There was a sacral decubitus ulcer. Evidences of acute bronchopneumonia, chronic cystitis, prostatic hypertrophy and a carcinoid of the ileum were found.

Adrenal: Gross examination. In one gland there was a grape-sized nodule of a bright yellow color in contrast to the rest of the tissue, which had a darker grayish hue. No traces of hemorrhages or cavitation were observed.

Microscopic examination. There was considerable fibrosis of the pericapsular tissue. The arteries showed atheromatous plaques. No ganglions were found; the nerves showed no round cell cuffing. There was hyalinization of the capsular collagenous fibrils, and lymphocytes infiltrated the subcapsular zone. The cortex and medulla showed an irregular line of junction. The large adenoma was entirely within the gland, and a sharp border between cortex and adenoma was formed by compressed, acidophilic cells and delicate fibrous stroma. The zona glomerulosa was irregular and narrow and in some areas entirely absent. The cells were small with wrinkled nuclei. Thickened radial septums traversed the cortex. The zona fasciculata was barely recognizable; only a few atrophic trabeculae were left, and the site of others was indicated by empty columns and fragments of cells. Nodules formed by large acidophilic cells produced further distortion (fig. 7). The cells showed all stages of disintegration; an occasional spongiocyte could be seen, but there were few lipid granules in even the best preserved cells. The zona reticularis consisted of fairly large cells with granular and at times vacuolated cytoplasm and many brown pigment granules. Many degenerating cells were seen, and round cells were scattered throughout. In the capillaries there was patchy engorgement. The adenoma consisted mainly of large foamy cells, whose contents stained pink with nile blue sulfate. The architecture seemed chiefly trabecular, with more medullary areas formed by densely packed acidophilic cells showing scanty lipids in a fine granular dispersion. The medulla was represented by a few nests of pheochrome cells, which were large and stained well. Cortical nodules clustered about the central vein, which showed decided muscular hypertrophy.

Case 4.—The patient was a 61 year old white woman. The duration of the disease was about four and a half months.

Nine weeks before being admitted to the hospital, this woman with hypertension and diabetes had a vesicular and bullous eruption, which healed and recurred. One week before she was admitted, oral lesions developed. There were noticeable malaise and progressive weakness. Physical examination revealed a generalized bullous eruption. The blood pressure was 180 systolic and 100 diastolic. Examination of the blood showed sugar, 250 to 93 mg.; nonprotein nitrogen, 27 mg., urea nitrogen, 11 mg., and cholesterol, 390 mg. per hundred cubic centimeters. The diabetes was controlled. The temperature was irregular and rose gradually. Death occurred on the seventy-second hospital day.

Autopsy.—A generalized eruption involved the skin and the oral and vulvar mucosa. There was a sacral decubitus ulcer. Evidences of early bronchopneumonia, cloudy swelling of the liver and kidneys, acute splenic hyperplasia and fibromyomas of the uterus were found.

Adrenals: Gross examination. There was decided irregularity in thickness. The tissue was friable, but no traces of hemorrhages or cavitation were found.

Microscopic examination. A small sympathetic ganglion showed no changes, but eccentric patches of lymphocytes were found along emergent nerve bundles. There were many extracapsular nodules of cortical cells, which at times extended loosely into the surrounding areolar tissue. There were atherosclerosis and calcification of the peripheral arteries. The capsule was irregularly thickened, and nests of cortical cells, lymphocytes and fibroblasts were found in the thickened areas. The zona glomerulosa showed decided interstitial fibrosis. The cells were very small. The zona fasciculata varied in width and architecture. Nodular hyperplasia was greatly in evidence. Occasional trabeculae were intact, and others were disintegrated and showed advanced necrosis of the parenchyma. The intact cells were small and uniformly depleted of lipids, and no spongiocytes were found. The zona reticularis was entirely absent in spots. Numerous fissures were seen. The parenchymal cells were small and necrotic. Bacterial emboli were common, and patches of lymphocytes were found. The medulla was patchy and interspersed with cortical tissue.

Case 5.—The patient was a 60 year old white man. The duration of the disease was about six months.

About five months before he was admitted to the hospital, a "pimple" appeared on the nose and grew rapidly. Other lesions appeared and spread rapidly, becoming generalized. There was decided malaise, severe itching at times and a disagreeable odor. Physical examination showed otherwise normal conditions. The course was steadily downhill and the patient died on the twenty-fifth hospital day.

Autopsy.—The skin was covered with bullae up to 4 inches (10 cm.) in diameter, some with fleshy, shiny bases and others with black crusts. Evidences of minimal bronchopneumonia, toxic myocarditis, prostatic hypertrophy, perisplenitis and esophageal varices were found.

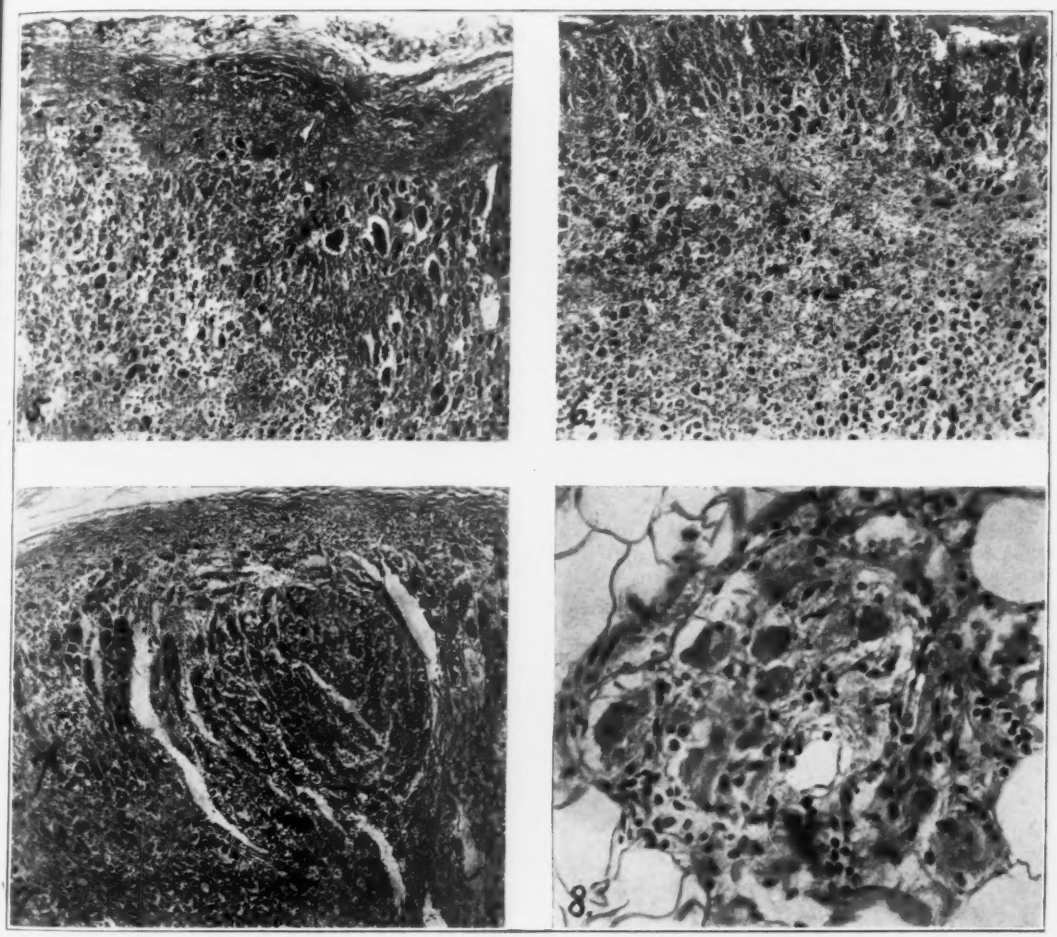

Fig. 5 (case 2).—Complete destruction of the cortical architecture with beginning fibrosis of the capsule and the glomerular layer. Mallory's acid fuchsin stain.

Fig. 6 (case 5).—Complete rebuilding of the cortex, with extensive cell loss and cirrhosis. Mallory's acid fuchsin stain.

Fig. 7 (case 3).—Large hyperplastic nodule, showing the same degenerative changes as the surrounding parenchyma. The arrow indicates a clump of round cells. Hematoxylin and eosin stain.

Fig. 8 (case 5).—Small sympathetic ganglion surrounded by lymphocytes and plasma cells. Hematoxylin and eosin stain.

Adrenals: Gross examination. Advanced cavitation was found, but there was no sign of hemorrhage. The color was a homogeneous buff throughout.

Microscopic examination (fig. 6). There were many extracapsular cortical nodules. A small sympathetic ganglion was surrounded by round cells (fig. 8). The capsule was thick and the collagenous fibers densely hyaline. The zona glomerulosa was broad with the stroma greatly increased. The cells appeared small and depleted of lipid, though occasional spongiocytes were seen. In the zona fasciculata a few columns were still intact; many had disappeared entirely, leaving empty spaces, or had disintegrated into individual decaying cells. Nodular hyperplasia formed groups of intensely staining cells. Occasional lymphocytic foci were seen. The zona reticularis was destroyed in most places by cavitation and fissuring, but a few of the intact cells contained large lipid droplets and the capillaries were intensely engorged. The medulla showed no changes. A large ganglion within the medulla showed degenerative changes of the ganglion cells.

CASE 6.—The patient was a 50 year old Negro woman. The duration of the illness was about eight months.

Seven months before the patient was admitted to the hospital, a generalized bullous eruption developed. On admission she also had a purulent conjunctivitis.

Laboratory examination revealed slight albuminuria, a positive reaction (4 plus) to the Wassermann test, a nonprotein nitrogen content of 22 to 27 mg. and a blood sugar level of 87 to 105 mg. per hundred cubic centimeters. The course was progressively downhill, with a constant, low grade fever rising terminally to 103 F.

Autopsy.—Generalized bullae alternated with areas of denudation and black hyperkeratotic skin. Evidences of bilateral bronchopneumonia, thrombosis of the cavernous sinus and left iliac, renal, ovarian and adrenal veins and fibromyomas of the uterus were found.

Adrenals: Gross examination. An anomalous left adrenal vein which was occluded by a friable thrombus was observed. The right adrenal was grayish, and the left was a brighter yellow. There were no hemorrhages or cavitation.

Microscopic examination. The peripheral vessels of the left adrenal were engorged, and one capillary showed a bacterial embolus. Many extracapsular nodules of cortical tissue were seen, some proliferating loosely into the adjacent areolar tissue. Ganglions and nerve bundles were surrounded by patches of round cells. The capsule showed irregular thickening and increased collagen, while the tissue of the left adrenal showed beginning infarction. The zona glomerulosa was narrow, with the cells being small and depleted of lipid. The stroma was decidedly increased. The zona fasciculata was distorted by nodules of cortical cells and by the disappearance of single cells or entire columns (fig. 2). The remaining cells were small and basophilic, and occasional cells within the nodules contained lipids. The cells of the left adrenal were somewhat larger, and occasional spongiocytes could be seen. The zona reticularis where present consisted of disintegrating cells bearing pigment granules. There was considerable capillary engorgement in the left adrenal. The medulla showed no architectural changes. Small organized thrombi, occasionally calcified, were seen bilaterally.

COMMENT

It is at once apparent that in all 6 cases extensive and decidedly similar changes were manifest. These may be grouped as follows: acute degenerative and inflammatory changes, necrobiosis and loss of cells, depletion of lipid, nodular hyperplasia and fibrosis. They demonstrate a definite pattern of development. Thus the wedge-shaped areas of necrosis seen in case 1 and the intense round cell infiltration of case 2, coupled with the minimal nodular hyperplasia in both cases and the beginnings of fibrosis in case 2, are fully consistent with the relatively short duration of the disease. Cases 3 to 6 indicate that the longer the course of the disease the more pronounced are the fibrosis and nodular regeneration. These changes are evidences of continued damage to the adrenals leading to scarring and attempts at regeneration, which finally produce a pattern comparable to the changes of hepatic architecture in Laënnec's cirrhosis. However, there was more hyperplasia in case 5 than in case 6, but an absolutely rigid parallelism with the duration of the disease is hardly to be expected. Generalized depletion of lipid, dimin tion of the size of the cells and diffuse degen ative changes of the parenchyma were found all 6 cases, and they imply important functio changes.

In addition, the round cell infiltration abo the small sympathetic ganglions and nerves is interest. This infiltration was in evidence in cases; in a fifth case only a few nerve bundl showed the change, and in the sixth no ganglio could be found but the nerves showed no infi tration. It is true that small foci of round cel are to be found within almost any adrenal an can hardly be considered abnormal, but infiltra tion of the nerve elements seems unquestionab pathologic. At the present time, any explanatio of this fact would be purely speculative. Othe changes, such as degeneration of the medullar ganglion cells in case 5 and old thrombi an fresh thrombosis and infarction in case 6, are t be considered as incidental. The presence o bacterial emboli in 2 cases is apparently termina in view of the absence of inflammatory reaction and does not explain changes which were als present in areas where no bacteria were found.

Although the lesions in all 6 cases were strikingly similar, there is nothing to indicate that they were either specific or pathognomonic. Lucien and Parisot[18] illustrated histologically almost identical tissue, presumably not from a person with pemphigus, in their description of the sclerosing, atrophic process which occurs in the adrenals during chronic infectious diseases of all sorts. They stated that they had seen essentially similar changes in tuberculosis, but during my experience I have not seen such changes. Garb[19] found biochemical evidence of adrenal cortex insufficiency in a case of bullous mycosis fungoides. In a single case (nonbullous) which I have observed at autopsy no degenerative changes or depletion of lipid was found.

It must be pointed out that the lesions found in this series could not be due to any concomitant infection which existed at the time of death. It is true that loss of lipids, fissuring and cavitation, as well as lymphocytic infiltration, are commonly seen in persons with acute infectious diseases, particularly bronchopneumonia.[20] However, hemorrhages into the cortex or the changes re-

18. Lucien, M., and Parisot, J.: Les glandes surrénales et organes chromaffines, Paris, 1913, p. 289, fig. 74.

19. Garb, J.: Mycosis Fungoides with Bullous Lesions: Special Tests and Laboratory Data Indicating Adrenal Insufficiency, Arch. Dermat. & Syph. **49**:315-320 (May) 1944.

20. Oppenheim, R., and Loeper, M.: L'insuffisance surrénale experimentale par lésions des capsules, Compt. rend. Soc. de biol. **55**:330-332, 1903.

ently described by Rich [21] as characteristic of acute infections are conspicuously absent in all my cases. Moreover, the occurrence of wedge-shaped necrosis does not belong to the picture of ordinary infection, nor does the diffuse disintegration of the zona fasciculata or the extensive loss of architecture.

In view of these observations it is hardly surprising to note the development of Addison's disease after pemphigus, especially when the regenerative ability of the adrenals seems to have been defective. Balbi's "nodular, interstitial suprarenitis" [11] is apparently identical with the picture I have observed. The frequently noted, less definite findings of "small necrotic areas," [3] "atrophy," "hypoplasia," [16] "nodular hyperplasia" [6] and "postmortem autolysis" become highly suggestive, and the "initial fibrosis of the reticularis" of Chiale,[13] which he apparently erroneously interpreted as a postmortem change, seems simply a less advanced stage of the process seen in figure 1. Thus one seems justified in assuming that careful histologic examination of the adrenals in persons with pemphigus will yield positive, significant findings far more consistently than the literature seems to indicate.

A cortex deprived of its lipid load and showing cell necrosis and deranged architecture is hardly capable of adequate secretory function. This does not necessarily mean that production of hormones has ceased altogether but merely that there are quantitative and perhaps qualitative changes.

Certain correlations can be drawn between the evidence of impairment of the adrenal glands and the clinical picture of pemphigus. It is known that in adrenal cortical insufficiency there is a decreased resistance to infection.[22] There is also an increased permeability of the capillaries, as a result of which plasma escapes from the blood stream.[23] This fluid is usually taken up into the intracellular compartment with no trend to edema, but with local changes in the skin it may possibly contribute to the formation of vesicles and Nikolsky's sign.

The biochemical changes in patients with pemphigus are not unequivocal. The decrease in urinary excretion of chlorides first noted by Krieger [1] has been corroborated by other investigators.[24] The serum chloride, as determined by various investigators,[25] was found to be high, low or normal. These discrepancies apparently represent different stages or degrees of adrenal involvement. At any rate, the findings of Talbott and others [3] show that in exacerbations of acute pemphigus the electrolyte pattern of the blood is almost identical with that in an addisonian crisis: An increase of nonprotein nitrogen and plasma potassium is accompanied by a corresponding fall in sodium and chloride. It is remarkable that these studies revealed increased volumes of blood, plasma and interstitial fluid in patients with both acute and chronic pemphigus as long as cutaneous lesions were present. These observations, which do not fit into the present concept of adrenal insufficiency, cannot be explained adequately and may be due to other factors unrelated to the adrenal lesions.

It must be emphasized that pemphigus is by no means a primary adrenal disease; on the contrary, the causative agent of pemphigus produces damage to the adrenals as a complication of the cutaneous disease. This complication, however, as in many other diseases, may contribute greatly to the symptomatology, course and eventual outcome of the disease.

SUMMARY AND CONCLUSIONS

The changes in the adrenals in 6 cases of pemphigus are described.

Regressive changes were present in all cases, and the extent of interstitial changes was commensurate with the duration of the disease.

The changes described are compatible with the view that the function of the adrenal is impaired in persons with pemphigus.

21. Rich, A. R.: Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse, Bull. Johns Hopkins Hosp. **74**:1-15 (Jan.) 1944.

22. Pottenger, F. M.: Neural and Endocrine Factors in Bodily Defense, Endocrinology **21**:449-454 (July) 1937.

23. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, Am. J. Physiol. **129**:691-697 (June) 1940.

24. Zorn, R., and Popchristoff, P.: L'élimination urinaire des chlorures dans les affections bulleuses et vésiculeuses de la peau, Ann. de dermat. et syph. **5**:667-696 (July) 1934. Cassaet and Micheleau.[2]

25. Urbach, E.: Zur Pathochemie des Pemphigus, Arch. f. Dermat. u. Syph. **150**:52-70, 1926. Kartamischev, A.: Ueber die Oedembereitschaft bei Pemphigus vegetans, ibid. **143**:184-192, 1923. Berhardt, R.: Weitere Beiträge zur Ätiologie des Pemphigus und der Dühringschen Krankheit, ibid. **171**:536-555, 1934. Talbott, Lever and Consolazio.[3]

CUTANEOUS AND SUBCUTANEOUS LESIONS OF THE LOWER LIMBS IN CONNECTION WITH THE VEINS

DIFFERENTIAL DIAGNOSIS

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In a great many dermatoses the limitation of eruptions to certain areas is often dependent on the distribution of the blood vessels in these regions. The relationship manifests itself either in an increased susceptibility to localized outbreaks or, more rarely, in a tendency to suppression.[1] This observation can be substantiated by demonstration of cutaneous lesions in close proximity to superficial visible veins (fig. 1) or to subcutaneous palpable veins. Infra-red photography[2] or phlebography[3] reveals the relationship between cutaneous lesions and concealed venous channels. The topographic coincidence may be visualized on any part of the body, but it is more apparent in areas with prevalent vascular disturbances, as, for example, on the lower extremities where, owing to generally unfavorable mechanical conditions, congestion easily develops. Hemostasis, even of slight degree, favors the appearance of cutaneous eruptions on the legs. The aggravation of symptoms corresponds to the progressive impairment of the venous circulation.

Severe and permanent changes are to be expected as a consequence of long-standing varicose veins. Chronic stagnation not only interferes with the adequate nutrition of the affected areas but also increases the tendency to recurrent phlebitis and inflammatory reactions in the perivenous tissues. The surface of an entire limb may become modified by ensuing atrophic or, more frequently, hypertrophic changes. Cutaneous lesions accompanying the "varicose symptom complex" may deviate from their usual clinical aspect, and difficulties may be encountered in their interpretation.

The recognition of the etiologic role of the veins in the development of all cutaneous manifestations of the limbs is important not only from the diagnostic but also from the therapeutic standpoint. The early treatment of the deficient circulation may prevent further complications and save the patient much discomfort in the future.

Fig. 1.—Scleroderma en bandes along varicose veins.

SYMPTOMS AND SIGNS OF BEGINNING HEMOSTASIS

One of the first signs of venous stasis, of increased capillary pressure and of capillary per-

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Abramowitz, E. W., and Isaak, L.: Lichenoid Amyloidosis: Report of Two Cases Featuring Absence of Cutaneous Lesions Over Some of the Tributaries of the Internal Saphenous Veins, Arch. Dermat. & Syph. **40**:13 (July) 1939.

2. Zimmerman, L. M., and Rattner, H.: Infra-Red Photography of Subcutaneous Veins, Am. J. Surg. **27**: 502 (March) 1935. Haxthausen, H.: Infra-Red Photography of Subcutaneous Veins, Brit. J. Dermat. **45**: 506 (Dec.) 1933.

3. Wolf, M., and Remenovsky, F.: Die praktische Anwendung der Varicographie, Wien. klin. Wchnschr. **44**:353 (March 13) 1931.

ineal ity may be edema of the dependent parts of the leg concomitant with pruritus. Itching is localized chiefly around the ankles, on the inside of the legs or on the shins. It increases toward evening after a day's work in an occupation that requires prolonged standing. Tiny papules are scattered among reddish discolored areas of the lower extremities; some of the lesions are covered with blood-stained brownish crusts; frequent scratching facilitates the gradual transition to eczematization.

Other cutaneous disorders may simulate these early stages of inadequate function of the veins. Lichen planus limited to the legs must be considered, but typical lichen planus lesions appearing later on the cheeks or in the genital regions or histologic examination which discloses the well known features of lichen planus will help to confirm the diagnosis.

Scratch marks confined to the legs may occur in persons with diabetes and may occasionally be mistaken for symptoms of hemostasis. Examination of the urine, determination of the blood sugar level or a high glucose tolerance curve will determine the true nature of the intense pruritus.

Some phases of blood dyscrasias manifesting themselves as prurigo on the lower limbs may be difficult to differentiate from hemostatic disturbances. Tiny itchy papules spread over a diffuse scaly dermatitis will not reveal the characteristics of leukemia, but repeated blood counts showing an increase of lymphocytes and a histologic picture of an enlarged lymph node will afford sufficient evidence for a diagnosis of prurigo lymphatica.

Another misleading sign in association with stasis is the occurrence of intracutaneous petechiae and pigmentations. Pinpoint-sized to pinhead-sized reddish spots changing to greenish brown and finally to dark brown usually form discrete nummular patches on all parts of the leg but mostly on the lower third. These ill defined lesions have a superficial resemblance in distribution and appearance to Schamberg's progressive pigmentary dermatosis and to the pigmented purpuric lichenoid dermatitis of Blum and Gougerot. But in Schamberg's disease,[4] observed more often among men, one finds first the same reddish puncta which, by extending in size and by uniting with other lesions, develop slowly into irregularly contoured reddish brown eruptions. The patches may be marked by exaggerated skin lines and by satellite lesions, so-called cayenne pepper spots, at the outer borders. The puncta gradually disappear, leaving a brownish discoloration. However, real petechiae are always missing. Furthermore, the absence of subjective sensations and of any form of dermatitis in the affected areas of the leg and, finally, the microscopic picture will support the diagnosis of Schamberg's disease. And in persons with pigmented purpuric lichenoid dermatitis[5] the lesions are pinhead-sized, elevated and papular, with the formation of flat, generally dark red plaques resembling lichen planus plaques. The individual papules do not enlarge peripherally and are discrete and regular; they later become purpuric and pigmented. Although the morphologic and clinical features of the aforementioned diseases are fairly distinctive and the histologic picture is well defined, some dermatologists believe that Schamberg's disease and pigmented purpuric lichenoid dermatitis are merely odd forms of stasis dermatitis.[6] The coexistence of superficial intracutaneous venules or telangiectases and the finding of deeper-seated varicosities by palpation will be additional criteria in favor of dermatitis hemostatica.

Purpura (Majocchi)[7] and angioma serpiginosum[8] may have a remote resemblance to gravitational dermatitis.

All these purpura-like diseases of the lower limbs are favorite topics of discussion among dermatologists, and the issues are not definitely settled. For instance, Goeckerman[9] has stated the belief that "Schamberg's disease, angioma serpiginosum and purpura annularis telangiectodes (Majocchi's disease) represent merely a terminology covering certain reasonably definite morphologic cutaneous pictures. They represent varying degrees of injury resulting from an internal toxin with predilection for the capillaries."

4. Templeton, H. J.: Progressive Pigmentary Dermatosis (Schamberg), Arch. Dermat. & Syph. **16**:141 (Aug.) 1927.

5. Wise, F., and Wolf, J.: Pigmented Purpuric Lichenoid Dermatitis, Arch. Dermat. & Syph. **31**:445 (April) 1935.

6. Laymon, C. W., in discussion on Rattner, H., and Falk, A.: Pigmented Purpuric Lichenoid Dermatitis of Gougerot and Blum, Arch. Dermat. & Syph. **47**:455 (March) 1943. Ayres, S., Jr., and Anderson, N. P.: Purpuric Lichenoid Dermatitis of Gougerot and Blum, ibid. **37**:1062 (June) 1938.

7. McKee, G. M.: Purpura Annularis Telangiectodes, J. Cutan. Dis. **33**:129, 186 and 280, 1915.

8. Wise, F.: Angioma Serpiginosum, J. Cutan. Dis. **31**:725, 1913.

9. Goeckerman, W., in discussion on Ayres, S., Jr.: Case for Diagnosis (Schamberg's Progressive Pigmentary Dermatosis?), Arch. Dermat. & Syph. **44**:927 (Nov.) 1941.

VARICOSE SYMPTOM COMPLEX AND SEQUELAE [10]

Valvular insufficiency tends to increase the reverse blood flow and the hydrostatic back pressure. Varicose degeneration and dilatation of the veins extend to the smallest superficial branches, and the resistance of the tissues to trauma and infection becomes lowered by the consequent chronic edema. Eczematous conditions and ulcer formation are the outstanding features of the varicose state; phlebitis and periphlebitis may precipitate their development. The different stages of varicose eczema are characterized by branny scaling, or flakelike exfoliation alternating with moisture and crust formation. Bacteria and fungi find an excellent medium for propagation in the permanently engorged legs. Dermatophytosis between the toes or of the nails serves as a source of repeated reinfection of the limbs. Secondary infections by streptococci in the form of lymphangitis or attacks of recurrent erysipelas may be followed by enormous swelling of the legs. Even without these infections the chronic inflammation of the superficial layers of the skin may slowly spread to deeper parts of the cutis and to the subcutis and may produce hyperplastic tissue changes. The state of pseudoelephantiasis may be accompanied with verrucous or papillary projections of skin.

Generalized cutaneous allergic reactions are often encountered as a consequence of chronic varicose eczema or varicose ulcers. The clinical picture may be confused by concurrent fungous infections of the feet, by sensitization to topical medicaments, such as sulfathiazole, or by any type of contact dermatitis. The detection of the responsible allergen and its elimination may be of great assistance in the improvement of generalized dermatitis in connection with varicose veins, although the final cure in some cases may be effected only after treatment of the degenerated veins.

IMPAIRED VENOUS CIRCULATION AS A CAUSATIVE FACTOR OF NEURODERMATITIS OF THE LEGS

Patients susceptible to atopic eczema may demonstrate the topographic coincidence of neurodermatitis with varicosities. The usual type of neurodermatitis, which is characterized by leathery exfoliating patches, may be found on the inside of the knee joint surrounding the dilated greater saphenous vein or along the course of degenerated tributaries. In some cases the veins may be detected better by palpation than by inspection.[11] In its early stage neurodermatitis of the limbs may be cured by elimination of incompetent feeding veins.

Lichen chronicus simplex (Vidal) may also exhibit the close connection with varicose veins. Frequent vigorous rubbing of the congested areas of the limbs causes flat polygonal shiny lichenoid papules or hard spherical nodular elevations which may be aggregated into extensive patches above the inner aspect or around the outer aspect of the ankle corresponding to the origin of the saphena magna or the saphena parva vein

Fig. 2.—Neurodermatitis associated with an incompetent lesser saphenous vein.

(fig. 2). Lichen chronicus simplex should be distinguished from localized primary amyloidosis and from lichen planus verrucosus.

Prurigo nodularis, a severer variant of neurodermatitis, may develop as a final result of intense scratching caused by hemostasis. Hypertrophic, hard, extremely itchy, tumor-like nodules with a verrucous surface are found close to varicose veins on a generally lichenified base (fig. 3). With the treatment of surrounding

10. Nobl, G.: Der varicöse Symptomenkomplex; seine Grundlage und Behandlung, Berlin, Urban & Schwarzenberg, 1918.

11. Heyerdale, W., and Cannon, E. E.: Neurodermatitis Associated with Incompetent Greater Saphenous Veins, Arch. Dermat. & Syph. **44**:52 (July) 1941.

varicosities these nodules may occasionally diminish in size or may even disappear.

VARICOSE THROMBOPHLEBITIS

One of the most frequent complications of varicosities is superficial thrombosis or thrombophlebitis promoted by the prevailing degenerative changes of the venous inner lining and by retardation of the blood stream. (Superficial varicose thrombophlebitis must be differentiated from thromboangiitis obliterans and from the migrating type of infectious thrombophlebitis.) Circulating bacteria in the anoxemic and congested veins may precipitate the development of varicose thrombophlebitis. Slight injury is not a causative factor but may be an exciting agent in inducing the outbreak of the dormant inflammation. The thrombophlebitic process manifests itself along very small veins as a circular patch but more often along the larger veins as a superficial indurated tender cord with redness of the overlying skin. If aneurysmal pouches of the wall of the vein are involved, dark bluish plum-sized prominent elevations may result.

Fig. 3.—Prurigo nodularis lesions close to varicose veins.

Varicose thrombophlebitis can be regarded as a natural healing process leading finally to obliteration of degenerated and useless blood vessels. Induration, atrophy and pigmentation of the tissues about the veins are common sequelae of the phlebitic process. The thrombotic veins at times become impregnated with calcium deposits so that hard formations, so-called phlebolites, are felt along the sclerosed varicosities. Recanalization may occur, reestablishing the former state of elongation and tortuosity. Repeated phlebitis of superficial varicosities may be followed by rarefaction of the wall of the vein and formation of linear channels covered by whitish atrophic skin with hyperpigmentation at the borders. The veins and surrounding tissues in patients with secondarily infected varicose thrombophlebitis are apt to break down and form punched-out ulcers resembling ulcerated erythema induratum (Bazin) or syphilitic ulcers (fig. 4).

Fig. 4.—Thrombophlebitic ulcer resembling exulcerated erythema induratum.

DEEP PHLEBITIS AND SEQUELAE

Postoperative or puerperal phlebitis is entirely different from superficial varicose thrombophlebitis. It is essentially, though not exclusively, limited to the deep veins. Severe pain, fever, rigor and swelling of the entire leg are outstanding symptoms. This type of phlebitis is

also called milk leg or phlegmasia alba dolens. Residual edematous changes and the appearance of superficial compensatory varicosities may depend on the degree of recanalization of the deep veins. Phlebography offers a reliable diagnostic criterion to determine with certainty the patency of the deep venous circulation after phlebitic processes.

The former shape of the affected limbs may occasionally be restored after subsidence of the acute symptoms. However, the permanent diffuse brownish purple discoloration and the tendency to repeated attacks of cellulitis are confirmatory evidence of the irreparable damage to the return circulation of the veins and lymph channels. The waterlogged tissues may gradually become atrophic and fibrotic. Ulcers in these undernourished parts of the leg may be called real phlebitic ulcers, which resemble ulcers occurring in dermatosclerosis.

Fig. 5.—*A*, ulcerated dermatosclerosis resembling idiopathic scleroderma; *B*, ulcerated idiopathic scleroderma with lilac-colored ring at the borders.

PERIVENOUS PACHYDERMA OR DERMATOSCLEROSIS

Perivenous pachyderma or dermatosclerosis is a special type of inflammatory process which starts insidiously in the periphery of smaller, deeper-seated varicosities. The inflammation becomes visible by the establishment of a brownish, indurated, palm-sized plaque on the leg above the inner side of the ankle, which may last indefinitely, with gradually increasing tenseness. The area may change its color to dark brown; it may become depressed below the surrounding surface by fixation to the subjacent tissues, and the inflammation may advance to the anterior and lateral aspect or may even continue to the upper third of the leg. Cufflike constrictions of sclerotic skin are characteristic features of this disease. Periostitic thickenings similar to those in tertiary syphilis may be perceptible.

This chronic progressive induration, which almost always is associated with varicose veins, is called by German authors "dermatosclerosis," and by French authors pachydermite; it was described by G. Nobl [12] under the name of *perivenöse Pachydermie*. Gaugier [13] explained it

12. Nobl, G.: Das verkannte Zustandsbild der perivenösen Pachydermie, Med. Klin. **31**:580 (May 3) 1935.

13. Gaugier, L.: Pathologie de l'appareil circulatoire (coeur et vaisseaux), in Rogen, G. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine, Paris, Masson & Cie, 1933, vol. 3, pt. 10, pp. 577-593 and 665-714.

as a microbic infection of the connective tissue without involvement of the veins and called it "cellulite." Biegeleisen,[14] who termed it "fibrolymphedema," assumed that the phlebitic infection extends to the perivenous tissues and involves the lymph channels and that complete blockage of the thrombosed lymph vessels causes chronic lymphedema, consequent hypertrophy of the connective tissue and finally fibrosis.

The sclerotic atrophic tissues are liable to break down and form chronic ulcers. If dilated or hardened veins are found in or above the involved areas the whole picture is easily understood, but diagnostic difficulties may arise if superficial varicosities are missing. The resemblance to localized scleroderma is occasionally striking, especially if the indurated parts become depigmented (fig. 5 *A*). Localized scleroderma, however, is more ivory colored, and the borders are usually sharp and round and are often surrounded by a lilac-colored ring (fig. 5 *B*). Typical morphea patches may be seen on other parts of the body, whereas fibrolymphedema is present only on the lower limbs and is poorly demarcated.

PHLEBITIS-LIKE NODULAR LESIONS OF THE LOWER LIMBS

It is a well known fact that the same cutaneous reaction may be produced by a number of agents; this holds true for nodular and ulcerating lesions around the veins of the leg. The causative factors may be various bacterial embolic processes or toxic and chemical influences. The lesions are mainly inflammatory reactions about the thrombotic veins, but in different phases the nodules may assume the clinical aspect of varicose thrombophlebitis involving the smaller veins and subsequent ulcerations may simulate varicose ulcers.

Erythema induratum (Bazin) usually starts on the posterior surface of the lower limb at the transition to the middle third, but lesions are also found on the lateral and outer aspects of the legs and, more rarely, on the thighs and arms. Globular, hard cutaneous-subcutaneous nodules, the size of a hazelnut, are discernible by palpation. The confluence of single nodules may lead to the development of cordlike or beadlike formations resembling thrombophlebitic indurations. The nodules may disappear by resorption without leaving a scar, but usually the overlying structures become involved and larger infiltrated patches are formed. This stage may be similar to the starting phase of the aforementioned perivenous pachyderma. The nodules inside the plaques tend toward superficial necrosis, resulting in deep punched-out circular ulcers with clearcut borders or in irregular superficial cavities with undermined edges, always with some degree of infiltration and purplish discoloration at the borders. This induration at the periphery is not so frequently observed in thrombophlebitic ulcers. Healing in erythema induratum is accompanied with the appearance of round depigmented cicatricial areas with hyperpigmentation at the borders.

Erythema induratum is generally considered to be of a tuberculous nature. Confirmation will be found in the usual presence of a tuberculous focus in the patient, in the positive reaction to tuberculin in all dilutions and in the coexistence of papulonecrotic tuberculids. But some authors refute the causative relationship of tuberculosis to erythema induratum. Telford,[15] for instance, expressed the opinion that Bazin's disease is not tuberculous and is in no way different from erythrocyanosis. The two diseases may occur in the same position on a fat and cyanotic leg when the limb is exposed to cold, and their clinical courses are exactly the same. Other authors, including O'Leary,[16] regard disease of the blood vessels, probably of the veins, as a significant factor in the cause of erythema induratum. The quick response of symptoms to the application of Pará rubber bandages has been stressed by O'Leary as proof for this theory. According to my experience, the weak peripheral circulation is only a predisposing factor for the development of erythema induratum in women and girls who are obliged to stand a great deal. In the same way concomitant varicosities may increase the tendency to recurrent outbreaks. The nearly symmetric distribution over the legs, the clinical course, the morphologic features and, finally, the histologic observations are sufficient to distinguish erythema induratum from chilblain affections and from all phlebitis-like nodular inflammations about the veins of the limbs.

Erythema nodosum may occasionally simulate the patchy form of phlebitis. It may also resemble erythema induratum, but the outer aspects of the limbs are preponderantly affected and the eruptions run a more acute course. Erythema nodosum does not end in ulceration, and there is no scarring or depression after regression of the nodules.

14. Biegeleisen, H. L.: Lymphedema Occurring with Varicose Veins, Arch. Dermat. & Syph. **33**:689 (April) 1936.

15. Telford, E. D.: Lesions of the Skin and Subcutaneous Tissue in Diseases of the Peripheral Circulation, Arch. Dermat. & Syph. **36**:952 (Nov.) 1937.

16. O'Leary, P. A., in discussion on Ebert, M. H.: Case for Diagnosis (Erythema Induratum), Arch. Dermat. & Syph. **48**:343 (Sept.) 1943.

VARICOSE ULCERATIONS OF THE LEG AND THEIR DIFFERENTIATION

The morphologic features of cutaneous ulcerative lesions of the legs are as variable and diversified as their underlying pathologic conditions. According to McPheeters [17] and Ochsner,[18] the defective return circulation is the main causative factor for nearly 80 per cent of the ulcers. Other investigators deny the relationship between ulcerations of the limbs and the impaired venous circulation. For instance, Becker [19] found that many patients with ulcers of the leg do not have varicose veins and most of the patients with varicose veins do not have ulcers. Different factors have to be taken into consideration in defining the cause of chronic ulcerative lesions of the limbs.

The detection of varicosities may occasionally be difficult. In some instances venous valvular insufficiency may be present without obvious change of thickness and form of the vein. However, palpation and percussion tests and the Trendelenburg test may prove the incompetence of the veins.[20] Furthermore, the varicosities may be hidden in stout persons or in patients with swollen limbs. In order to bring these varicose trunks into prominence, bandaging or rest in bed will be found useful. In other cases the varicose state is limited to deeper-seated small or medium-sized veins which form a network of dilated communicating branches and which are not recognized by direct observation. Phlebography may reveal these deep venous channels.[21] Occasionally in persons with perivenous pachyderma the originally distended veins shrink to sclerotic cords which may be found by deep palpation. The connection of some ulcers, such as "phlebitic ulcers," with the deficient venous circulation may be overlooked, since their formation takes place five or even ten years after subsidence of acute symptoms, but an accurate history will diminish the margin of error. The development of varicose ulcers generally depends on the type and severity of the varicosities and the occupation of the patient. Trauma or a minimal infection from scratching are sufficient to initiate extensive and long-lasting ulcerations. Profuse bleeding of superficial varicosities may be the preliminary symptom of ulcers in the region of the ankle.

The close association of ulcerative lesions with varicosities can easily be traced when so-called feeder or key veins arise in their neighborhood (fig. 6). Soft elevations representing venous pools may be felt beneath or adjacent to the ulcers, or the draining veins may become noticeable only after complete healing of the cavities. There are usually dermatitis and pigmentation

Fig. 6.—Varicose ulcers with feeding varicose veins.

at the periphery of the ulcers. Chronic inflammatory changes may occasionally extend to the periosteum and even to the bones. Onychogryphosis may be symptomatic of the chronic inflammation.

Constitutional disorders may influence the shape and duration of ulcers of the leg in older people. De Takáts [22] observed that 50 per cent of his patients with varicose veins also showed

17. McPheeters, H. O., and Anderson, J. K.: Injection Treatment of Varicose Veins and Hemorrhoids, ed. 2, Philadelphia, F. A. Davis Co., 1943.

18. Ochsner, A., and Mahorner, H.: Varicose Veins, St. Louis, C. V. Mosby Company, 1939.

19. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1943, p. 277.

20. McCallig, J. J., and Heyerdale, W. W.: A Basic Understanding of Varicose Veins, J. A. M. A. **115**:97 (July 13) 1940.

21. DeBakey, M.; Schroeder, G. F., and Ochsner, A.: Significance of Phlebography in Phlebothrombosis, J. A. M. A. **123**:738 (Nov. 20) 1943.

22. de Takáts, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929.

diminished arterial supply, which is partly responsible for the decreased resistance of the tissues to trauma. The preponderance of arteriosclerotic changes over involvement of the veins can be proved by tests like the Samuel postural test, palpation of the pulse, a roentgenogram of the arteries and oscillometric readings. Nephritis, heart disease or cirrhosis of the liver may be contributing factors to the chronic engorgement of the legs.

Diagnostic problems may arise if the typical features of the varicose ulcerations become changed by other concomitant pathologic states. The most common ulcers to be distinguished from varicose ulcers are syphilitic ulcerations of the tertiary stage.[23] Tuberculous, malignant and mycotic ulcerative lesions must be excluded. Gangrenous pyoderma and ecthyma, ulcers due to ingestion of drugs and ulcers associated with sickle cell anemia and idiopathic colitis should be recognized. Tropical ulcers, Gallipoli sore,[24] yaws and leishmaniasis must also be considered in the differential diagnosis of varicose ulcerations.

The correct interpretation of all these chronic ulcerations of the leg and the recording of evidence disclosing their underlying causative factors are of preeminent importance.

23. Ochsner, A.: Chronic Cutaneous Ulceration of the Lower Extremities, New Orleans M. & S. J. **84**: 594 (Feb.) 1932.

24. Vischer, A. L.: Das Wüstengeschwür, Schweiz. med. Wchnschr. **72**:1436 (Dec.) 1942.

SUMMARY AND CONCLUSIONS

The close connection of cutaneous and subcutaneous lesions of the legs with the deficient venous circulation is often overlooked. Aggravation of symptoms corresponds to the progressive impairment of the venous circulation and the relationship may be confirmed by the quick response of cutaneous manifestations to the elimination of degenerated venous channels. Correct interpretation and differentiation of cutaneous changes caused by hemostasis may be facilitated by tests for incompetency of the veins and by infra-red photography or by phlebography. A roentgenogram of the veins will help to prevent the diagnosis of deep phlebitis in various diseases of the legs of obscure origin.

Extensive fibromatosis of the legs, which is a characteristic feature of "perivenous pachyderma," may be occasionally encountered after deep phlebitis. The fibrotic state in both diseases may be explained by the chronic damage to the venous and lymph channels and by reactive hyperplastic tissue changes about the vessels. Ulcerations developing in the two conditions are much alike.

Chronic ulcerative lesions of the legs are caused in nearly 80 per cent of cases by varicosities. The deficient venous circulation may be regarded as a contributing factor in the development of certain cutaneous diseases of the legs, as, for instance, erythema induratum.

969 Park Avenue.

DERMATITIS VENENATA

FOLLOWING USE OF PENICILLIN OINTMENT

LIEUTENANT COMMANDER LEONARD SIMPSON MARKSON (MC), U.S.N.R.

It has been previously noted that penicillin when administered parenterally gives rise to varied cutaneous manifestations,[1] such as urticaria, recurrent vesicular eruptions and exfoliative dermatitis. A case of contact dermatitis [2] has been reported in a medical officer who was preparing penicillin.

To these cases of penicillin sensitivity I shall add a case of dermatitis venenata which developed in a white man following treatment for mild conjunctivitis with penicillin ointment.

REPORT OF A CASE

The patient was admitted to the sick list at another hospital complaining of swelling about the eyes and face. The onset was three weeks before, when he noted a slight burning and irritation of the eyes, but no accompanying redness or injection. A diagnosis of mild conjunctivitis was made.

He was given some eye drops for a couple of days, without relief of symptoms. He then used a 5 per cent sulfathiazole ointment for ten days, but there was still no change in his condition. Then a penicillin ointment was placed in his eyes, and on the following morning the patient noticed edema of the eyelids and surrounding tissue. The ointment was discontinued for one day and then reapplied, with more severe edema and erythema about the eyes and upper part of the face resulting.

On Feb. 12, 1945 the patient was transferred to this hospital with the history given. Results of examination were essentially negative except for edema and an erythematovesicular dermatitis of the eyelids and the entire periorbital region, extending down to the lower end of the nose and cheeks. There was a slight purulent discharge in the palpebral fissures. Conjunctivas, scleras and corneas appeared normal.

A diagnosis of dermatitis medicamentosa was made. Medication was stopped, and compresses of boric acid solution were applied every hour. Sodium thiosulfate, 1 Gm., was administered intravenously. The dermatitis regressed with great rapidity, and the patient was discharged as cured on February 19. He returned to his original place of duty, where, at my request, patch tests were made with the sulfathiazole and penicillin ointments previously employed. These tests were applied to the patient's back on February 23,[3] and were removed twenty-four hours later. There was a negative reaction to the sulfathiazole. The area tested with the penicillin ointment showed an erythematous, vesicular eruption, the size of a half dollar, surrounded by a zone of edema. This was associated with some burning and itching which lasted for three days. After seven days there was still some scaling of the skin in that area. The eyelids and surrounding tissues were not affected. Many other patients have been treated with the ointment used on this patient, and no reactions have been observed. Unfortunately the patient was transferred to another activity before he could be tested with the various components of the ointment bases, which in each preparation were: wool fat 5 per cent, white wax 5 per cent and white petrolatum 90 per cent.

SUMMARY

A case of dermatitis venenata of the eyelids and face following the use of penicillin ointment is reported.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the authors and are not to be construed as reflecting the policies of the Navy Department.

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2. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 9) 1944.

3. Carr, R. M.: Personal communication to the author.

NEW CUTANEOUS BACTERICIDAL AGENT USED IN SOAP

FURTHER PRACTICAL STUDIES

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In a recent study [1] we investigated the cutaneous bactericidal properties of 2,2′-dihydroxy-3,5,6-3′5′, 6′-hexachlorodiphenylmethane [2] (hereinafter termed G-11) when incorporated in a toilet soap to the amount of 2 per cent,[3] and found that the routine daily use of this germicidal soap made it possible to reach and maintain an exceedingly low bacterial population on the skin of the hands and forearms. We especially wish to direct attention to the fact that this result can be achieved only by using G-11, or some other equally effective germicide, in a soap or other suitable detergent that is used exclusively by the individual each and every time he has any occasion to use soap for any purpose whatsoever. We stress this point particularly because since our recent publication [1] we have been deluged with requests for information concerning soap to be used for operating room scrub-up. G-11 soap is effective for this purpose *only if it is exclusively used* by the surgeon every time he uses soap and water for each and every washing. This important principle had apparently not been thoroughly understood. Conducting our investigations according to a method modified [1] after those of Price,[4] Pohle and Stuart,[5] and Pillsbury [6] and others, we compared the effect of this agent with 70 per cent (by weight) alcohol, a commercial soap claimed to be germicidal (neko) and a standard surgical scrub-up technic, by hand washing experiments on a large scale. This study included experiments which showed that G-11 was nonirritating to the human skin, as shown by over four hundred individual patch tests.

We are herewith reporting on additional experiments designed to prove that 2 per cent G-11 soap had produced a truly bactericidal rather than bacteriostatic action and that it does not form a film on the skin under which viable bacteria are retained in large numbers. The effect of G-11 soap on pathogenic cutaneous organisms was also included in this study.

QUESTION OF FILM FORMATION

Miller and his associates [7] have shown by experiments that washing the hands with the use of a germicidal cationic detergent such as zephiran chloride leaves the skin apparently free from bacteria, but subsequent washings with an anionic soap releases large numbers of live bacteria, thus suggesting the presence of an imperceptible film of the cationic substance. Alcohol, alum and mercuric salts have also been observed to produce protective films masking viable organisms.

We reasoned that if a film formed by a cationic soap is broken by the use of an anionic soap, the opposite should also take place. Therefore, if anionic soap containing compound G-11 would form a film on the skin, then this film should be removable by subsequent use of a cationic soap, and this should result in a flora

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2. William S. Gump, U. S. Patent 2,250,480.

3. The soaps used in these experiments were supplied by Givaudan-Delawanna, Inc., New York.

4. Price, P. B.: The Bacteriology of Normal Skin, J. Infect. Dis. **63**:301, 1938; New Studies in Surgical Bacteriology and Surgical Technic, with Special Reference to Disinfection of Skin, J. A. M. A. **111**:1993 (Nov. 26) 1933.

5. Pohle, W. D., and Stuart, L. S.: The Germicidal Activity of Rosin Soap and Fatty-Acid Soap as Indicated by Hand Washing Experiments, Oil and Soap, **18**:2, 1941; The Germicidal Action of Cleansing Agents, J. Infect. Dis. **67**:275, 1940.

6. Pillsbury, D. M.; Livingood, C. S., and Nichols, A. C.: Bacterial Flora of the Normal Skin: Report on Effect of Various Ointments and Solutions, with Comments on Clinical Significance of This Study, Arch. Dermat. & Syph. **45**:61 (Jan.) 1942.

7. Miller, B. F.; Abrams, R.; Huber, D. A., and Klein, M.: Formation of Invisible, Nonperceptible Films on Hands of Cationic Soaps, Proc. Soc. Exper. Biol. & Med. **54**:254, 1943.

of normal numbers. We set up an experiment on this basis.

Six subjects washed through the standard ten-basin washing procedure, using control soap (anionic). Three of the subjects substituted Onyxsan S 1 per cent (a surface active agent of the alkyl amidoalkyl amidoazoline type) and the remaining 3 subjects zephiran chloride 1 per cent in basin 5 for the control soap. Onyxsan S and zephiran chloride are cationic detergents; the former is nonbactericidal, while the latter is a potent germicide. The results are shown in table 1.

TABLE 1.—*Number of Organisms on Skin After Use of Anionic Control Soap and Cationic Detergent*

Cationic detergent was used in basin 5, anionic control soap used in all other basins. Subjects I, II and III used zephiran chloride, and subjects IV, V and VI used Onyxsan S in basin 5.

	Basin									
Subjects	1	2	3	4	5	6	7	8	9	10
I	883	741	224	244	6	229	132	128	64	64
II	475	302	174	228	1	68	53	82	90	86
III	262	154	98	80	7	66	38	39	28	25
IV	85	126	101	98	411	65	78	46	42	37
V	653	523	133	403	393	133	113	96	76	56
VI	825	418	333	331	484	313	152	94	95	69

Actual counts per basin may be obtained by multiplying the numbers by 10,000.

In a second experiment 6 subjects washed through the standard ten-basin washing procedure, using control (anionic) soap and each subject was given a bar of 2 per cent G-11 (anionic) soap with instructions to use only this soap for all washings of the skin for the following week and then to return for the final washings. The final washings were conducted as follows:

Three subjects washed for a two minute period, using a 1 per cent aqueous solution of Onyxsan S, and rinsed in basin 1. Washing with control (anionic) soap then followed in the other nine basins. The remaining 3 subjects went through this same routine, except that 1 per cent zephiran chloride was used instead of Onyxsan S. The results are shown in table 2 and the chart.

TABLE 2.—*Number of Organisms on Skin After Use of G-11 for a Week*

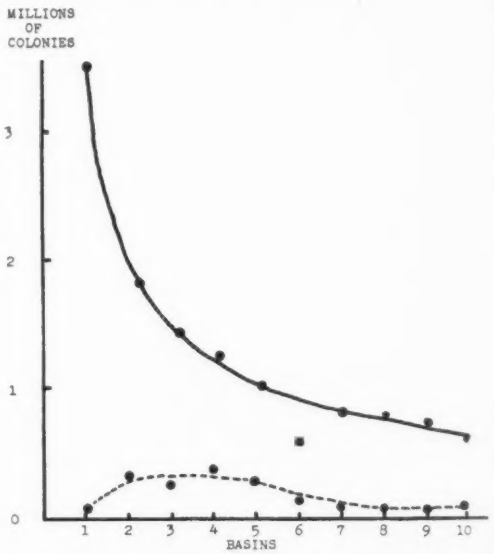
Cationic detergent was used in a two minute washing prior to basin 1. Subjects I, II and III used zephiran chloride and subjects IV, V and VI used Onyxsan S; 2 per cent G-11 (anionic) soap had been used by all subjects routinely for one week previously.

	Basin									
Subjects	1	2	3	4	5	6	7	8	9	10
I	0	15	21	13	18	11	3	9	2	12
II	0	91	93	90	63	48	38	18	24	27
III	2	9	8	7	3	6	2	2	1	1
IV	1	8	2	4	2	7	1	4	1	3
V	1	91	69	115	79	47	38	35	44	71
VI	17	9	12	6	7	2	5	5	5	4

Actual counts per basin may be obtained by multiplying the numbers by 10,000.

Referring to table 1, there will be noted an obvious difference in the action of zephiran chloride and Onyxsan S. It would appear that zephiran chloride kills those bacteria which are removed in basin 5, but, as is shown, the count returns to a high level as soon as the cationic film is removed by anionic soap in basins 6 to 10. Thus zephiran chloride apparently has only a superficial action and simply covers the bacteria temporarily with a removable film. These results agree with the findings of Miller and his associates.[7] Onyxsan S, which is nongermicidal, has an action similar to that of the ordinary anionic soaps. After G-11 (anionic) soap is used for one week, it does not matter whether zephiran chloride or Onyxsan S is used before the final washing (table 2). The counts are equally low and not higher than in the previous experiments, in which no cationic detergent was applied prior to the washings with control soap.

Obviously, if our premise is correct, G-11 does not exert its apparent action in reducing the resident bacterial flora of the skin by obscuring the bacteria beneath a film. This substantiates the opinion that G-11 acts by actually killing the bacteria on and in the skin; in other words, 2 per cent G-11 soap does not produce a protectant film on the skin, a condition which would give rise to a false sense of security.



Results of experiments. The unbroken line shows results when control (anionic) soap was used in all basins. The broken line shows results of final washings when subjects had used 2 per cent G-11 soap for one week. Cationic soap "film removing detergent" was used in basin 1; control soap was used in the last nine basins.

THE ROLE OF BACTERIOSTASIS

We felt certain that any trace of G-11 soap left on the skin following its routine use over one week and possibly carried over in the rinsings obtained from control soap washings would be so negligible that it could exert no bacteriostatic effect in the still more dilute cultures made from these rinsings.

However, in order to prove this point conclusively, cultures were made of the rinsings obtained in the control soap washings after the routine use of 2 per cent G-11 soap for one week, by plating 1 cc. and 0.1 cc. samples from each basin. These results are shown in tables 3, 4, 5 and 6. If bacteriostasis is not a factor, then the ratio of the number of colonies obtained in these two plates should be of the order of 10:1. If G-11 carried over does cause bacteriostasis in a certain dilution, then the bacteriostasis should be lessened by increasing the dilution of G–11.

TABLE 3.—*Control Soap Washings Prior to Routine Use of 2 per Cent G-11 Soap*

Subjects	Size of Sample	Basins 1	2	3	4	5	6	7	8	9	10
I	0.10 cc.	327	276	260	179	252	171	158	172	113	125
	0.01 cc.	35	43	25	21	14	22	17	18	15	11
II	0.10 cc.	141	200	156	140	81	78	79	162	53	52
	0.01 cc.	15	21	19	18	8	10	9	5	2	8

Actual counts per basin may be obtained by multiplying counts as shown by 20,000 for the 0.1 cc. samples and by 200,000 for the 0.01 cc. samples.

TABLE 4.—*Control Soap Washings Following a Week's Routine Use of 2 per Cent G-11 Soap*

Subjects	Size of Sample	Basins 1	2	3	4	5	6	7	8	9	10
I	1.00 cc.	86	1	41	25	27	23	11	17	13	101
	0.10 cc.	13	0	3	4	1	3	5	0	1	14
II	1.00 cc.	126	195	96	92	46	43	22	23	21	16
	0.10 cc.	19	17	11	8	5	2	2	3	5	4

Actual counts per basin may be obtained by multiplying counts as shown by 2,000 for the 1 cc. samples and by 20,000 for the 0.1 cc. samples,

The series of ten basins for each subject has been added together in order to simplify the foregoing findings:

TABLE 5.—*Control Soap Washings Prior to Routine Use of 2 per Cent G-11 Soap*

Figures show total number of colonies of all basins added together.

Subjects	Grand Total Counts 0.1 Cc.	0.01 Cc.	Ratio	Average Ratio
I	2,028	221	10:1.1	10:1.1
II	1,142	125	10:1.1	

TABLE 6.—*Control Soap Washings Following a Week's Routine Use of 2 per Cent G-11 Soap*

Figures show total number of colonies of all basins added together.

Subjects	Grand Total Counts 1 Cc.	0.1 Cc.	Ratio	Average Ratio
I	345	44	10:1.3	10:1.2
II	680	76	10:1.1	

Therefore, if we can obtain counts of the same ratio regardless of the dilution bacteriostasis is not involved.

It is readily seen in table 6 that the ratio obtained in the two dilutions after the routine use of 2 per cent G-11 soap is approximately the same as the ratio obtained in the two dilutions prior to the use of the 2 per cent G-11 soap.

The remote possibility that the extremely small amount of compound G-11 which could be carried over from the skin to the basins and then to the cultures exerts a bacteriostatic action is entirely excluded by these findings; hence the low counts obtained in control soap washings following the routine use of 2 per cent G-11 soap are not due to bacteriostasis.

EFFECT ON PATHOGENS

The question had been brought up as to whether 2 per cent G-11 soap kills the pathogenic portions of the cutaneous flora as well as the nonpathogenic organisms. We have attempted to answer this question by a procedure using Staphylococcus aureus as an example of the pathogenic flora. Because Staph. aureus is usually found on 10 per cent of human skins, because it is an accepted organism in evaluating the potency of germicides, and because of the relative ease with which it is identified, we decided to use its disappearance from the cutaneous surface as an indicator of effectiveness of G-11 soap on pathogens.

Accordingly, the skin on the dorsa of the hands of 207 industrial employees was swabbed to obtain carriers of Staph. aureus. Staph. aureus was identified as such by finding several colonies of a gram-positive coccus which produces a golden pigment, hemolyzes blood agar and gives a positive reaction to the coagulase test. From 8 persons who were found to be carriers of Staph. aureus at the first swabbing cultures were taken at intervals of at least one week in order to establish definitely a carrier state, and they were then given bars of 2 per cent G-11 soap to use in all washings for a period of ten days. Any subject on whom Staph. aureus could be found on at least two of the three swabbing dates prior to the routine use of 2 per cent G-11 soap was considered a proved carrier. The skin of these persons was again swabbed two times after the routine use of G-11 soap was ended, and cultures were made to determine the presence or absence of Staph. aureus. The results are shown in table 7.

In is interesting to note that subject 47 ran out of 2 per cent G-11 soap three days before the swabbing on August 11 was done. It is possible that he reestablished his pathogenic flora during

this interval. A study of table 7 shows that 2 per cent G-11 soap was effective in removing Staph. aureus in 7 out of 8 cases of proved carriers. This suggests an efficiency of 87.5 per cent and warrants the assumption that the routine use of 2 per cent G-11 soap is equally effective in removing pathogenic and nonpathogenic bacteria from the human skin.

TABLE 7.—*Presence or Absence of Staph. Aureus on Skin of Carriers After Routine Use of G-11 Soap*

Subject	5/19	7/13	8/1		8/11	8/22
202	+	+	—	All	—	+
86	+	—	+	subjects	—	+
89	+	—	+	used	—	+
174	+	—	+	2% G-11	—	—
165	+	+	+	soap	—	+
118	+	+	—	during	—	—
47	+	+	—	this	+	+
195	+	+	+	interval	—	+

SUMMARY AND CONCLUSIONS

1. Two per cent dihydroxyhexachlorodiphenyl methane (G-11) incorporated in toilet soap enabled the subjects studied to maintain an exceedingly low bacterial population on the skin of the hands and forearms.

2. Compound G-11 was nonirritating to the skin as judged by more than four hundred patch tests. These were repeated on the same subjects after ten to fourteen days and were again found to be negative, showing that no sensitivity of the skin had been produced by the first tests. Subjects using 2 per cent G-11 soap regularly for one year have shown no evidence of irritation.

3. Our hand washing experiments (121 individual series of washings) indicate that the most significant results were obtained by the regular daily routine use of 2 per cent G-11 soap. The evidence indicates that the exclusive use of toilet soap containing compound G-11 in a concentration of 2 per cent has such an effect on the bacterial flora of the human skin that the so-called resident bacteria are decidedly and permanently (as long as this soap is used) exclusively reduced in number. A person using this soap regularly each time his hands are washed has a lower resident count after two minutes of washing than one who washes for twenty minutes with ordinary toilet soap. The striking bactericidal effects obtained by daily use of toilet soap containing compound G-11 compared with regular use of ordinary or control soap and neko soap, a commercial soap claimed to be germicidal, indicate its value.

4. These results lead us to conclude that the *daily and exclusive* use of a soap containing compound G-11 would enable a surgeon or operating room attendant to maintain an extremely low resident bacterial population on his skin.

5. Experiments prove that 2 per cent G-11 soap does not form a film which would retain a large number of live bacteria beneath it.

6. The remarkably lowered resident flora following the routine use of 2 per cent G-11 soap has not resulted from bacteriostasis but from actual killing.

7. Two per cent G-11 soap when used exclusively is an efficient agent in reducing the number of both pathogenic and nonpathogenic organisms found on the human skin.

8. Exclusive use of soap containing compound G-11, according to our experiments, should reduce the probability of infection following abrasions and superficial wounds of the skin. This point might be of value in the hygienic care of members of the armed forces. Attendants of wounded in front line areas where lengthy surgical scrub-up routines which include the use of alcohol and iodine may be out of the question could nevertheless feel that the resident bacterial populations on their hands were at an exceedingly low level.

9. The use of G-11 either in soap or in other vehicles for protection against cutaneous infections from barber shops and beauty parlors, hair follicle infections from cutting oils, etc., is suggested.

DERMATITIS MEDICAMENTOSA ASSOCIATED WITH SECONDARY POLYCYTHEMIA

REPORT OF A CASE

SAUL S. ROBINSON, M.D., AND SAMUEL TASKER, M.D.

LOS ANGELES

Polycythemia is known to occur as a disease entity of unknown cause, primary polycythemia,[1] and as a relative or symptomatic transient disorder of the red blood cells secondary to various diseases. Primary polycythemia has been described as associated with deep pruritic infiltrative cutaneous lesions and a generalized papular eruption (acne urticata polycythaemica[2]). No record, however, could be found in the dermatologic literature of the association of symptomatic or relative polycythemia with a dermatologic disease. The following case is therefore reported as an example of symptomatic or secondary polycythemia associated with a cutaneous disease, dermatitis medicamentosa.

REPORT OF CASE

History.—N. J., an 18 year old Jewish clerk, was first seen on Aug. 9, 1943, because of a generalized red itching eruption. The history revealed that one week previously he had received a subcutaneous injection of procaine hydrochloride and zylcaine as local anesthetics during the surgical treatment of external hemorrhoids. No other drugs were administered. Twenty-four hours after the injection a fine red itching rash appeared on the face. The eruption became more pronounced and pruritic during the next three days and spread to the neck, trunk and extremities. The pruritus was intense and the face, neck and upper part of the chest became noticeably swollen and indurated. Discrete red papules and papulovesicles appeared on the cheeks. The face became so swollen that the patient had difficulty in opening his eyelids and mouth. He stated that when he was 11 years old he had a severe local and febrile reaction following the administration of tetanus toxin-antitoxin.

Physical and Dermatologic Examinations.—The physical examination revealed normal conditions. The heart rate was 120, and the blood pressure was 125 systolic and 80 diastolic. The temperature was 101.5 F. The dermatologic examination revealed that the face, neck, trunk and extremities were covered with a bright erythematous macular and papulovesicular eruption. The face, neck and upper part of the chest were swollen and enlarged to about twice normal size. The swelling was so intense that the eyelids were tightly shut and the mouth could be opened only with difficulty. The facial features were distorted, and the skin of the swollen areas felt hard and indurated.

Laboratory Examination.—The examination of the urine showed a positive reaction for acetone. The serologic reaction of the blood for syphilis was negative. The examination of the blood on August 9 showed: hemoglobin content, 122 per cent (20.6 Gm.); erythrocytes, 6,930,000 per cubic millimeter; color index, 0.88, and leukocytes, 11,800 per cubic millimeter, with 86.5 per cent neutrophils, 1.5 per cent eosinophils, 8 per cent lymphocytes and 4 per cent monocytes.

On August 11 the hematologic examination showed: hemoglobin content, 104 per cent (17.6 Gm.); erythrocytes, 5,800,000 per cubic millimeter; color index, 0.91, and leukocytes, 8,900 per cubic millimeter, with 78 per cent neutrophils, 16 per cent lymphocytes, 4 per cent eosinophils and 2 per cent monocytes.

On August 17 the hematologic examination showed: hemoglobin content, 85 per cent (14.5 Gm.); erythrocytes, 5,180,000 per cubic millimeter; color index, 0.82, and leukocytes, 10,200 per cubic millimeter, with 68 per cent neutrophils, 23 per cent lymphocytes, 2 per cent eosinophils and 7 per cent monocytes.

Course.—After the initial examination, the swelling and induration of the face, neck and chest became greater for two days and then subsided entirely within one week. The facial features became normal, and the generalized pruritic eruption disappeared. The temperature varied from 101.5 to 100 F., and the pulse rate varied from 120 to 90 until the lesions subsided.

Treatment.—The treatment consisted in the application of cold compresses of dilute (1:16) solution of aluminum subacetate to the face and neck and of an antipruritic shake lotion to the trunk and extremities. Calcium gluconate, 15½ grains (1 Gm.), and 50 cc. of 50 per cent solution of dextrose were administered intravenously daily.

COMMENT

Symptomatic polycythemia, or erythrocytosis, must be differentiated from primary polycythemia. Primary polycythemia is an idiopathic disease of unknown cause associated with an absolute increase in the erythrocytes per cubic millimeter and an increase in the total red blood cell count. Symptomatic polycythemia, or erythrocytosis, is a transient disorder in which the total number of

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1. Vaquez, H.: Sur une forme speciale de cyanos s'accompanant d'hyperglobulie excessive et persistente, Compt. rend. Soc. de biol. **4**:384, 1892. Osler, W.: Chronic Cyanosis with Polycythemia and Enlarged Spleen: A New Clinical Entity, Am. J. M. Sc. **126**: 187, 1903.

2. Gans, O.: The Skin Picture in Hematopoietic Diseases, Arch. Dermat. & Syph. **16**:4 (July) 1927. Klauder, J. V.: Acne Urticata Polycythaemica, ibid. **38**:145 (July) 1938.

erythrocytes is normal although the number of red blood cells per cubic millimeter is increased. Relative or secondary increases in the number of erythrocytes are caused by a decrease in the plasma volume. This may result from fluid lost by the blood during various conditions, such as excessive perspiration and ventilation of the lungs (exercise), profuse diarrhea and severe vomiting. The action of bacterial and chemical toxic agents on the red blood cells and congenital heart disease may also cause secondary polycythemia. Among the chemical agents reported to cause polycythemia are tuberculin, epinephrine, digitalis, carbon monoxide, arsenic, caffeine and opium. No reference was found in the medical literature to symptomatic or relative polycythemia associated with procaine hydrochloride or zylcaine dermatitis. There is also no record of symptomatic polycythemia associated with the loss of plasma from the blood in cases of severe edema and inflammation of the skin and subcutaneous tissues due to a cutaneous disease, dermatitis medicamentosa. Zylcaine is a combination in purified peanut oil of local anesthetics, consisting of a procaine base, 1.5 per cent, butyl aminobenzoate, 6 per cent, and benzyl alcohol, 5 per cent.

Symptomatic, or secondary, polycythemia is a transitory condition, and definite improvement occurs by dilution of the blood with fluid or by reabsorption of the lost blood plasma in edematous areas, as in our patient's dermatosis. It is debatable whether the drug or drugs causing the dermatitis in our patient had any direct toxic action on the red blood cells. It is our belief that the secondary polycythemia was caused by an excessive loss of blood plasma associated with the severe edema and swelling and inflammation of the skin and subcutaneous tissues of our patient's face, neck and chest resulting from dermatitis medicamentosa.

SUMMARY AND CONCLUSIONS

A patient was encountered with dermatitis medicamentosa associated with secondary polycythemia.

Secondary polycythemia associated with dermatologic diseases can be caused by severe edema, swelling and inflammation of the skin and subcutaneous tissues resulting in decided loss of blood plasma.

Secondary polycythemia associated with a dermatologic disease, such as dermatitis medicamentosa, is a transitory condition that disappears when the edema and swelling of the skin and subcutaneous tissues clear.

1930 Wilshire Boulevard (5).

WATERHOUSE-FRIDERICHSEN SYNDROME

REPORT OF A CASE

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The disease known as the Waterhouse-Friderichsen syndrome was described as an entity by Graham Little [1] in 1901. He reviewed the literature and published 4 cases of his own. Waterhouse [2] reported his case in 1911 and reviewed 15 others. He gave an accurate description of symptomatology and pathology.

In 1918 Friderichsen,[3] in Germany, published his 2 cases and brought the literature up to date. There was little information as to the cause of the syndrome at this time. Maclagan and Cooke,[4] in 1916, were perhaps the first to label the meningococcus as the etiologic agent. Reports have been printed in the German literature concerning the entity by Baumann [5] and others. Aegerter [6] and Sacks [7] reviewed the literature in 1936 and 1937 respectively. Considerable publicity has been given to the syndrome during the last three to four years. Recent papers by Bush and Bailey [8] and Boger [9] have presented the current and up-to-date features of this entity.

The history, symptoms and sequence of events are so frequently repeated that the Waterhouse-Friderichsen syndrome is a definite entity. Most of the cases are usually seen in children under the age of 2 years. It is not infrequent in adults.

The characteristic clinical history usually states that the patient was well until the sudden attack of the disease. The early symptoms are nonspecific, and are those that might occur in any acute infection.

The first symptoms may be malaise, restlessness, chills, headaches or vomiting. Abdominal pain occurs in a high percentage of cases. There is hyperpyrexia of spiking septic type, with a temperature as high as 107 F. The patient soon becomes stuporous and lethargic and convulsions may develop.

Cyanosis is usually noted about eight to twelve hours after the onset. The lips and nails are blue and the skin is livid. This picture suggests the diagnosis of early pneumonia.

Petechiae follow the cyanosis, involving the face, trunk and extremities. The lesions appear suddenly, varying in size from small petechiae to larger purpuric macules. They occasionally become confluent, to form dark purple patches the size of an orange. Bush and Bailey [8] reported that their patients had conjunctival hemorrhage causing "bloody tears."

In twelve to twenty-four hours the patient is extremely toxic and semicomatose. Breathing is shallow and rapid; respiration may be Cheyne-Stokes type at the end. During the initial illness, the pulse is rapid in relation to the hyperpyrexia and later becomes feeble and thready. The blood pressure is usually low. Neurologic findings are not consistent. Headache is usually severe. Cervical rigidity may or may not be present. Reflexes usually are unchanged.

Netter and Salanier [10] first found meningococci in the smears from purpuric lesions. This

1. Little, E. G.: Cases of Purpura, Ending Fatally Associated with Hemorrhage into the Suprarenal Capsules, Brit. J. Dermat. **13**:445-467 (Dec.) 1901.

2. Waterhouse, R.: A Case of Suprarenal Apoplexy, Lancet **1**:577 (March 4) 1911.

3. Friderichsen, C.: Nebennierenapoplexie bei kleinen Kindern, Jahrb. f. Kinderh. **87**:109-125, 1918.

4. Maclagan, P. W., and Cooke, W. E.: Fulminating Type of Cerebro-Spinal Fever: Pathology and Causes of Death, Lancet **2**: 1054-1055, 1916.

5. Baumann, T.: Zur Aetiologie und Klinik der akuten Nebennierenblutungen und Hypoplasie), Ztschr. f. Kinderh. **51**:276-293, 1931.

6. Aegerter, E. F.: The Waterhouse-Friderichsen Syndrome: A Review of the Literature and Report of Two Cases, J.A.M.A. **106**:1715-1719 (May 16) 1936.

7. Sacks, M. S.: Fulminating Septicemia Associated with Purpura and Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome): Report of Two Cases with Review of the Literature, Ann. Int. Med. **10**:1105-1114 (Feb.) 1937.

8. Bush, F. W., and Bailey, F. R.: The Treatment of Meningococcus Infections with Special Reference to the Waterhouse-Friderichsen Syndrome, Ann. Int. Med. **20**:619-631 (April) 1944.

9. Boger, W. P.: Fulminating Meningococcemia: Demonstration of Intracellular and Extracellular Meningococci in Direct Smears of the Blood, New England J. Med. **231**:385-387 (Sept. 14) 1944.

10. Netter, A., and Salanier, M.: Présence des méningocoques dans les éléments purpuriques de l'infection meningococcique, Compt. rend. Soc. de biol. **29**:670-673, 1916.

was corroborated by McLean and Caffey,[11] who also found meningococci by direct smear in the purpuric lesions of 83 per cent of 18 cases of meningococcemia. Maclagan and Cooke[4] in 1916 were the first to classify the meningococcus with the syndrome. Sacks,[7] in reviewing the literature, stated that of 21 cases occurring between 1916 and 1937, in only 60 per cent was the meningococcus demonstrated.

The disease is extremely severe. At times leukocytosis with 8,000 to 90,000 white blood cells is seen. Bamatter[12] noted a shift to the left in the cells of the myelogenous series. The polymorphonuclear count may be as high as 95 per cent.

PATHOLOGY

Sacks stated that the most outstanding pathologic finding is a severe bilateral adrenal hemorrhage. This was seen in 95 per cent of the cases. Aegerter, in his review of the literature, found 52 cases in which there was bilateral adrenal hemorrhage. Microscopically destruction of the medullary tissue is seen, and many areas are replaced by extravasated blood. Several areas show complete obstruction of the three glandular layers. The purpura is probably due to the involvement of the capillaries and arterioles by the causative organism or its toxin. Other pathologic findings are similar to those of any severe acute infection.

PROGNOSIS AND THERAPY

Aegerter stated that the disease had been fatal in all cases described to 1936. Recently patients of Carey,[13] Rucks and Hobson[14] and Bush and Bailey have recovered.

The duration of the disease is usually about twenty-four to forty-eight hours. The overwhelming septicemia with its fatal hemorrhage is thought to be the feature of this entity.

The high mortality indicates that treatment is imperative and should be immediate, as a delay of several hours may be fatal. Aegerter suggests massive doses of cortical extract, epinephrine and intravenously injected dextrose and blood transfusions. Bush and Bailey added sulfadiazine intravenously and injection of desoxycorticosterone. One should combat anoxemia (when the patient is cyanotic) by the use of an oxygen tent.

REPORT OF CASE

History.—A 37 year old Filipino was seen on July 2, 1944, with a history of mild malaise, fever and chills and a suggestive purpuric rash on the trunk, arms and legs. The rash had been present only a few hours. His past history was irrelevant. A tentative diagnosis of erythema multiforme was made.

The patient was admitted to Queen's Hospital twenty-four hours later, complaining of a dull headache, slight nausea and occasional vomiting, with abdominal pain and muscular tenderness. He was conscious and partly aware of his surroundings.

Examination.—Examination showed a well developed man apathetic in appearance. The temperature was 99 F., pulse rate 98, respiration 28 and blood pressure 100 systolic and 70 diastolic. The pupils were equal and responded to light and in accommodation. The ocular fundi showed no papilledema. The nose and throat were slightly congested. The chest was clear. The heart was normal in size, rhythm, rate and sound. Deep and superficial reflexes were normal. The muscles of the extremities were tender on palpation. The abdomen was tense, tender and bloated. There was a diffuse macular purpuric rash with lesions varying in size from a few millimeters to that of a silver dollar. There were no lesions on the palms and soles.

Urinalyses gave normal results. Laboratory tests showed: hemoglobin 16 Gm., red blood cells 5,360,000, white blood cells 29,500, polymorphonuclears 94, lymphocytes 4, eosinophils 2, bleeding time three minutes and thirty seconds, platelets 375,690 and sedimentation rate 10 millimeters per hour. A blood culture was taken at this time.

Treatment and Course.—In a few hours the patient's condition became critical, as evidenced by cyanosis, delirium and a severe chill. The rectal temperature was 107 F., the pulse weak and thready, with a rate of 144 a minute. The blood pressure was 90 systolic and 60 diastolic. Respiration became labored. The patient was incontinent of stools and urine. The purpura became severe, with conjunctival hemorrhages resembling hemorrhagic tears.

Dr. A. S. Hartwell, an internist, was called in consultation and a diagnosis of acute septicemia, cause unknown, was submitted. This was substantiated by a hemogram by Dr. Kandel Hamre (hematologist).

The case puzzled us, as the sequence of events was not clear. That day the diagnosis of Waterhouse-Friderichsen syndrome was suggested by Dr. Stewart Doolittle in an informal discussion. The credit for saving this man's life can be given to Dr. Doolittle, as immediately adrenal cortex extract was given intramuscularly and 5 Gm. of sulfadiazine intravenously and 1 Gm. of sulfadiazine by mouth every four hours. Plasma was injected intravenously plus 5 per cent dextrose in

11. McLean, S., and Caffey, J.: Endemic Purpuric meningococcus Bacteremia in Early Life, Am. J. Dis. Child. **42**:1053-1074 (Nov.) 1931.

12. Bamatter, F.: Fulminante Meningokokkensepsis: Zur Aetiologie des Syndroms von Waterhouse-Friderichsen, Jahrb. f. Kinderh. **142**:129-162, 1934.

13. Carey, T. N.: Adrenal Hemorrhage with Purpura and Septicemia (Waterhouse-Friderichsen Syndrome) with Recovery: Case Report, Ann. Int. Med. **13**:1740-1744 (March) 1940.

14. Rucks, W. L., and Hobson, J. J.: Purpura Fulminans (Waterhouse-Friderichsen Syndrome): Report of a Case with Recovery, J. Pediat. **22**:226-232 (Feb.) 1943.

saline solution. Oxygen therapy was instituted for the cyanosis.

There was a dramatic change in the clinical picture in four hours after the aforementioned therapy was started. The temperature dropped from 106 F. to 98 F. in eight hours and wavered around 100 and 101.4 F. for several days. The pulse and respiration rates dropped to normal. The patient's color improved, and he appeared more alert. The purpura remained about the same for four or five days and gradually faded, leaving pigmentation. The only setback appeared three days later, with severe seizures of coughing. The diagnosis of early bronchial pneumonia was thought to be due to retained secretion and to the known hemoptysis. This rapidly cleared in a few days. Administration of adrenal cortex was stopped in five days, and sulfadiazine was discontinued on the sixth day of the illness.

Results of urinalysis remained within normal limits. Examination revealed: red blood cells 4,600,000, hemoglobin 14.6 Gm., white blood cells 13,200, polymorphonuclears 69, lymphocytes 16, eosinophils 13 and monocytes 2. The sulfadiazine level reached 17.5; the blood culture was sterile, and the spinal fluid was sterile after ten days. There was no occult blood in the stool.

The remainder of the convalescence was uneventful, and the patient returned to work in four weeks.

COMMENT

The Waterhouse-Friderichsen syndrome is a rarity in dermatologic literature but has been described in recent journals on internal medicine. Because of the early purpuric rash the dermatologist may be the first to see a case of this disease or may be called in consultation. The entity is now being recognized, and therapy must be started as soon as the diagnosis is established. In an epidemic of meningitis it is possible that a certain number of cases will be found which will have the clinical features of the Waterhouse-Friderichsen syndrome.

The adrenal hemorrhages seen in these fulminating septicemias have suggested that the cause of death is acute failure of the adrenal cortex. Hyperthermia, hypotension, vascular collapse, abdominal pain, vomiting, cyanosis and purpura are essential for the diagnosis. Meningococcic infections usually produce the syndrome, but overwhelming sepsis due to other organisms may give rise to similar adrenal hemorrhages. Boger states that not all patients who die with a clinical picture of Waterhouse-Friedrichsen syndrome present adrenal hemorrhages. Therefore Boger believes that it seems ambiguous to use the term "recovery" in speaking of a cure of Waterhouse-Friderichsen syndrome, since adrenal hemorrhage can only be suggested if the patient survives. He suggests the name "fulminating meningococcemia" in preference to Waterhouse-Friderichsen disease and that the latter should be restricted to pathologic discussions.

Dr. H. M. Izumi,[15] of the island of Maui, reports 2 cases of Waterhouse-Friderichsen syndrome occurring in Filipino plantation workers. The meningococcus was isolated by blood culture. Both patients survived because of early administration of penicillin intramuscularly and sulfadiazine intravenously. An interesting feature is the fact that both Filipinos were employed in the same gang and apparently were infected by one another or by another carrier.

Recently Cosgriff [16] found a decrease in the serum sodium and an increase in the nonprotein nitrogen, compatible with adrenal cortical insufficiency.

Acute severe septicemia initiates the disease; consequently rapid and adequate chemotherapy must be instituted. Sulfadiazine is the drug of choice and should be administered intravenously and subcutaneously and even by the oral route. Penicillin will probably be used. Adrenal cortex extract is helpful in combating the possible adrenal insufficiency. Continuous intravenous injection of fluid should be employed for circulatory collapse.

The increase in reports of cases of the Waterhouse-Friderichsen syndrome indicates a mild epidemic in certain areas. The syndrome is of interest to the dermatologist as well as to the internist. This common interest is also observed in acute disseminated lupus erythematosus and many other syndromes.

SUMMARY AND CONCLUSIONS

A case of Waterhouse-Friderichsen syndrome with recovery is reported.

The characteristic clinical history usually states that the patient was well until the sudden attack of the disease. The first reaction may be malaise, restlessness, chills, headaches or vomiting. Abdominal pain is of frequent occurrence. Hyperpyrexia may be severe. The patient becomes lethargic and stuporous and may have convulsions.

Cyanosis is usually noted eight to twelve hours after the onset. The skin is livid, and the lips and nails are blue. Petechiae appear and vary from small to larger purpuric macules.

In a few hours the patient is extremely toxic and semicomatose. The clinical picture is compatible with severe vascular collapse.

15. Izumi, H. M.: Personal communication to the author.

16. Cosgriff, S. W.: The Waterhouse-Friderichsen Syndrome: Observation on Associated Adrenal Insufficiency and Report of Four Cases, Ann. Int. Med. **21**: 187-193 (Aug.) 1944.

The meningococcus has been classified with the syndrome in many cases. Other organisms have been isolated in recent cases. It is not unusual to find normal blood in spinal fluid cultures.

The outstanding pathologic finding is a severe bilateral adrenal hemorrhage. There are destruction of medullary tissue and areas replaced by extravasated blood.

The high mortality indicates that treatment must be immediate. It is suggested that massive doses of adrenal cortex extract be given, also epinephrine, intravenously injected dextro blood transfusions, sulfadiazine intravenous and desoxycorticosterone. Anoxemia is to treated by use of an oxygen tent or similar the apy. Penicillin probably will be added to the l of therapeutic possibilities.

This syndrome will be seen by the dermatol gist, probably because of the purpura. T recognition of this disease entity within the fi twenty-four to forty-eight hours is imperative, the suddenness of death necessitates early dia nosis and therapy.

COLLOIDOCLASTIC SHOCK FOLLOWING INJECTION OF OXOPHENARSINE HYDROCHLORIDE (MAPHARSEN)

REPORT OF A CASE

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CHICAGO

The following case is reported because of the rarity of colloidoclastic shock and nitritoid reactions after the injection of oxophenarsine hydrochloride (mapharsen).

REPORT OF CASE

G. S., a white man aged 39, gave a history of having blastomycosis, apparently limited to the skin, of four years' duration. On examination in the University of Chicago Clinics on Dec. 15, 1944, he had presented numerous ulcerated infiltrates, measuring from 1 to 4 cm. in diameter, distributed over the back, thighs, left leg and right arm. Budding blastomycetes were found in direct smears of the pus expressed from these lesions. Biopsy section disclosed conditions compatible with a diagnosis of blastomycosis, but no micro-organisms could be demonstrated in the tissue.

The patient's general physical condition was good. Fluoroscopic examination of the chest showed no pulmonary involvement. Wassermann and Kahn tests elicited negative reactions. The white blood cell count was 8,800, and the hemoglobin content was 14 Gm. The urine was normal.

Since there was a history of sensitivity to iodides, it was decided to try arsenical therapy, as recommended by Stokes,[1] in addition to local roentgen ray treatment. The patient had never had arsenicals before. He was given 0.02 Gm. of oxophenarsine hydrochloride intravenously without any reaction on Dec. 23, 1944. On December 30 he was given the second injection of oxophenarsine hydrochloride, 0.03 Gm. by the usual intravenous technic. After this second injection he complained of pain along the entire arm; this was interpreted as venous cramping. However, he felt well enough to get off the table. Almost immediately he complained of feeling ill and became ashen gray; about one minute later he collapsed and stopped breathing. The eyes remained open, staring sightlessly. The skin was clammy, and perspiration could be seen on the face.

Artificial respiration was administered immediately. After about a minute the patient gasped. The gasping was repeated several times but with long intervening apneic periods. Finally, he began to breathe irregularly. During an interruption of artificial respiration, about three minutes after the onset of the reaction, 0.5 cc. of solution of epinephrine hydrochloride (1:1,000) was administered hypodermically. The pulse was thready but soon became full and slower, although it had a bigeminal character at first. The patient apparently recovered completely within one-half hour, but two days later he experienced severe pain in the back and in the right testicle and suffered from a severe headache which lasted for three days. He was last seen in this clinic on Jan. 6, 1945, one week after the shock reaction, feeling weak and having a slight amount of testicular pain. Subsequently, he was treated by his family physician with local heat, sodium thiosulfate, pyridium (phenylazo-alpha-diaminopyridine monohydrochloride) and sedation because of severe testicular pain which lasted about one week, and after that he was treated for severe pain over the region of the kidneys. Urologic examination, including cystoscopy, failed to reveal renal involvement. On February 3, the patient was doing well, according to a report from his physician.

COMMENT

Stokes, in his textbooks,[1] differentiates sharply between a nitritoid reaction and colloidoclastic shock. In the typical nitritoid crisis the patient is primarily "flushed, hyperactive, coughing, choking and with a bounding pulse," while in colloidoclastic shock he is "pale, pulseless and collapsed." However, according to the same author, in the final stage of the nitritoid vascular reaction the patient becomes unconscious, and he may also become pulseless and collapse. This last phase of the nitritoid crisis is rather similar to the syndrome of colloidoclastic shock. My patient had the symptoms of colloidoclastic shock and not those of the first stages of a nitritoid reaction. It is possible, however, that because of the severity of his reaction the final stage of nitritoid crisis was the only one observed.

In any case, a review of the literature reveals that both a nitritoid reaction and colloidoclastic shock following injection of oxophenarsine hydrochloride are rare. Levin and Keddie[2] reviewed the literature from 1935 to 1941, and although they reported the case of a patient displaying "shock, pallor, weakness, nausea and vomiting," they stated that no true nitritoid reaction was described. They reported, however,

From the Section of Dermatology, Department of Medicine, University of Chicago.

1. Stokes, J. H., and others: Fundamentals of Medical Dermatology, Philadelphia, University of Pennsylvania Department of Dermatology Book Fund, 1942, p. 350. Stokes, J. H.; Beerman, H., and Ingraham, N. R.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1944, pp. 151 and 409-411.

2. Levin, E. A., and Keddie, F.: Toxic Effects Following the Use of Mapharsen, J. A. M. A. **118**:368-372 (Jan. 31) 1942.

42 cases in which there were severe repeated nitritoid crises following the injection of arsphenamines and stated that these patients on the other hand tolerated oxophenarsine hydrochloride without any reaction resembling a nitritoid crisis.

Carter, Chambers and Anderson,[3] in a statistical review of all cases in the Navy and Marine Corps, Veterans Administration and native population of insular possessions in which oxophenarsine hydrochloride was used from 1935 to 1942 inclusive, reported only 1 severe vasomotor reaction (followed by death) from a total of 397,680 doses. However, resulting from 1,364,814 injections of neoarsphenamine, administered from 1925 to 1942, there were 63 severe vasomotor reactions, including 6 deaths; this is a ratio of 1 to 21,664. In 1942, resulting from 109,095 injections of oxophenarsine hydrochloride, there were 2 mild vasomotor reactions, but the described symptoms were not typical of nitritoid crisis or colloidoclastic shock.

3. Carter, T. J.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds, U. S. Nav. M. Bull. **42**:229-241 (Jan.) 1944.

Stokes, Beerman and Ingraham,[4] in a review of the literature on reactions to arsenicals in the treatment of syphilis, made no mention of nitritoid reaction following administration of oxophenarsine hydrochloride. Simon and Iglauer[5] described their patient's reaction to the first injection of oxophenarsine hydrochloride as "faintness almost to the point of syncope." Cole and Palmer[6] recorded 4 instances of vascular crisis or reaction resembling nitritoid reaction but stated that the notes in the charts of these patients were insufficient for them to draw a definite conclusion. No other instances of nitritoid reaction or colloidoclastic shock following injection of oxophenarsine hydrochloride were found in the literature available to me.

4. Stokes, J. H.; Beerman, H., and Ingraham, N. [illegible] The Trivalent Arsenicals in Syphilis, Am. J. M. S. **202**:606-624 (Oct.) 1941.

5. Simon, S. R., and Iglauer, A.: Death Following Mapharsen Therapy, Am. J. Syph., Gonor. & Ven. Dis. **23**:612-616 (Sept.) 1939.

6. Cole, N. H., and Palmer, R. B.: Mapharsen in the Treatment of Syphilis, Arch. Dermat. & Syph. **36**:561-580 (Sept.) 1937.

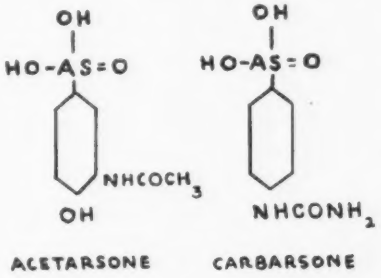
CARBARSONE IN THE TREATMENT OF PEMPHIGUS

A PRELIMINARY REPORT

ROBERT P. LITTLE, M.D.
NEW YORK

Arsenic, of all the drugs used in the treatment of pemphigus, has withstood the test of time. Although it has been condemned by a few investigators as being of no benefit or even harmful, in the majority of cases of patients reported improved or cured arsenic is the medicament most frequently mentioned. It has been employed as solution of potassium arsenite (U. S. P., sodium and iron cacodylate, old salvarsphenamine, neoarsphenamine, tryparsamide and others. Just why arsenic should be beneficial in treatment of pemphigus is not known. It may be parasiticidal, for it is an interesting observation that many of the preparations credited with "cures" have been protozoal poisons, such as quinine, antimony and potassium tartrate, Germanin and compounds such as tryparsamide and acetarsone. It seems more probable, however, that arsenic is merely a tonic acting on the nerves, gastrointestinal tract, reticuloendothelial cells, endocrine glands and skin. It is conceivable that some preparations may be more curative and less toxic than others, but only experimentation and knowledge of the cause of the disease will determine which is the best. Recently acetarsone has been the subject of keen interest because of favorable reports in the literature.

The first report on the use of acetarsone was made by M. Oppenheim[1] before the Viennese Dermatological Society in November 1927. In 1929 Kromayer,[2] in the *Deutsche medizinische Wochenschrift*, wrote of having obtained benefit in 6 cases of pemphigus, 2 of severe pemphigus, by the use of *spirozid* (acetarsone). He concluded that by treatment with acetarsone pemphigus, if not cured, loses its acute character and assumes a chronic inflammatory type. In 1943 Oppenheim and Cohen[3] reported good results from the use of the drug. Acetarsone is no. 594 in Ehrlich's series and is 3-amino-acetyl-4-hydroxyphenyl arsonic acid. It has been used in the prophylaxis and treatment of syphilis but has not attained extensive popularity because it is unreliable and toxic. It now finds its principal use in the treatment of congenital syphilis and amebic dysentery. However, the reports on its use for patients with pemphigus are encouraging (it is probably the best drug so far suggested); nevertheless, its toxicity would prompt caution in its use against a chronic disease for which treatment must be prolonged. Arsenical poisoning is said to occur in approximately 1 of 6 patients (when acetarsone is used against syphilis). A therapeutic axiom is, "First, do no harm." Patients ill of pemphigus are already depressed and toxic from disease.



Structural formulas of acetarsone and carbarsone.

An ideal arsenical to be used against a chronic disease should be well borne, of low toxicity, suitable for oral administration over a considerable time, of high therapeutic efficiency and yet of comparatively low price. For pemphigus, why not seek a preparation resembling acetarsone, which for some reason has proved to be effective?

It occurred to me that carbarsone, also a pentavalent arsenical (28.5 per cent arsenic), with a structural formula resembling that of acetarsone but much less toxic, was worthy of

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Department of Dermatology and Syphilology, Third Medical (New York University) Division, Bellevue Hospital, service of Dr. Frank C. Combes.

1. Oppenheim, M.: Pemphigus chronicus serpiginosus, Zentralbl. f. Haut- u. Geschlechtskr. **26**:350, 1927.

2. Kromayer: Sechs durch Spirozid geheilte (?) Pemphigusfälle, Deutsche med. Wchnschr. **55**:229, 1929.

3. Oppenheim, M., and Cohen, D.: Acetarsone in the Treatment of Pemphigus, Arch. Dermat. & Syph. **47**:40 (Jan.) 1943.

trial. Carbarsone (paracarbamidophenyl arsonic acid) was studied and introduced as an amebacide by Anderson and Reed [4] in 1931. It has also been used in the treatment of Trichomonas vaginalis infections. It is of low toxicity (one eighth that of acetarsone), is of high therapeutic efficiency (twelve times that of acetarsone) and is relatively cheap. Carbarsone has recently been admitted to the "Pharmacopeia of the United States" and is a pentavalent organic arsenical, insoluble in water but readily absorbed from the gastrointestinal tract and slowly excreted. It is contraindicated for persons with hepatic or renal disease, and, as with other pentavalent arsenicals, changes in vision should be watched for, though to my knowledge serious changes have not been reported. Local edemas, diarrhea, nausea, vomiting, abdominal pains and mild cutaneous eruptions have been observed. According to Goodman and Gilman,[5] carbarsone is one of the most innocuous of organic arsenicals, and deaths from its use have been extremely rare.

In April 1944, the use of carbarsone in the treatment of pemphigus was begun in Bellevue Hospital in the dermatologic service of Dr. Frank C. Combes. With the cautions and contraindications mentioned in mind and in order to avoid a cumulative effect, a scheme of intermittent dosage was adopted as follows: 1 or 2 (0.25 Gm.) capsules for three days (one-half hour before breakfast), followed by a rest for three days. Improvement with this schedule was noted after three or four weeks. In view of the slowness in improvement, a more intensive dosage could be tried in the beginning. A suggested schedule is 1 capsule (0.25 Gm.) twice a day for ten days, followed by a rest for ten days. This, in turn, is followed by the three day dosage and three day rest plan.

Since carbarsone is an arsenical and may prove to be hepatotoxic, a test of hepatic function should precede treatment and a blood count and urinalysis made once a week. As a further precaution, the visual fields may be examined and checked, though so far "despite the paraposition of the amido group serious optic damage is almost unknown." [5] Laboratory work, such as determinations of chloride level, sedimentation rate and albumin-globulin ratio and Pels-Mach tests, is interesting to help confirm the diagnosis and to follow the course of the disease as well as to afford a criterion for recovery.

The good results in this brief series of cases should not blind one to the fact that pemphigus is a most serious disease and that the third attack is usually fatal, in spite of encouraging remissions. A nourishing diet, vitamins, transfusions of blood and plasma, and above all the good nursing care that patients receive in this hospital are to be weighed and given the credit they deserve in the improvement in these cases. Routinely, patients received daily 50,000 U. S. P. units of vitamin A, 1 Gm. of brewers' yeast, 2 mg. of riboflavin, 50 mg. of ascorbic acid and 50 mg. of nicotonic acid.

COMMENT

Under the plan described, use of carbarsone has been continued to date without intermission except in a single case in which edema was noticed localized to the face and hands which disappeared with temporary discontinuance of the drug. Of 17 patients with pemphigus, 3 died, 6 have been discharged with the disease arrested, 5 are under treatment greatly improved and 1 was transferred to another service in an improved condition. Of those who died, some were moribund and all were in poor condition on admission. Among those discharged and those still under treatment are many who were seriously ill, 1 who had pemphigus vegetans, others who had widespread bullae and 1 who had deep bedsores.

CONCLUSION

Carbarsone is suggested for the treatment of pemphigus.

147 Avenue B.

4. Anderson, H. H., and Reed, A. C.: Amebiasis: Comments on Various Amebacides; Report of Case, California & West. Med. **35**:439, 1931.

5. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1940.

Clinical Notes

FEVER AND STERILE ABSCESS FORMATION ACCOMPANYING TREATMENT OF SYPHILIS WITH PENICILLIN

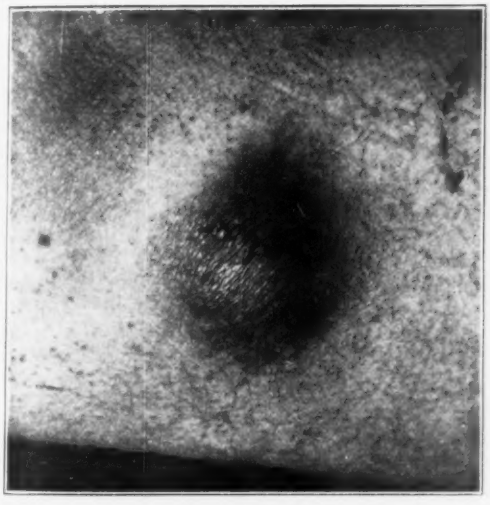
M. Edward Goebel, M.D., and Arthur W. Grace, M.D., Brooklyn

Mahoney [1] and Stokes,[2] with their collaborators, have reported the occurrence of fever and abscess formation in persons undergoing treatment for syphilis with penicillin. The case presented here includes features not mentioned by those authors.

REPORT OF A CASE

J. M., a white man aged 40, when first seen, on Jan. 15, 1945, had a nodular ulcerative syphilid on the extensor aspect of the right forearm which had been present for two years. The physical condition was good, and a general examination revealed no other abnormalities. The Wassermann reaction of the blood was 4 plus, and complete fixation of the complement occurred with 0.2 cc. of cerebrospinal fluid.

Therapy was commenced with oxophenarsine hydrochloride (mapharsen) and a bismuth preparation.



Bacteriologically sterile abscess over the great trochanter of the femur.

After four injections of the former and two of the latter had been given in ten days, treatment was suspended, owing to the development of chills, fever, nausea, vomiting and pain in the lower part of the back. Within two days this reaction had subsided, and therapy with oxophenarsine and bismuth was resumed, only to be abandoned entirely after a single injection of each drug had produced the same untoward effects. On this occasion the reaction was accompanied with epistaxis and was sufficiently severe to confine the patient to bed for four days.

On February 20, ten days after the subsidence of the reaction, treatment with penicillin was commenced, 25,000 oxford units being injected intramuscularly at three hour intervals. After twenty doses had been given, the patient's temperature rose to 103.2 F. in eight hours, and there was decided congestion and some edema of the soft palate, uvula, fauces and pharynx. Also, indurated, erythematous, edematous, painful areas, 4 to 6 inches (10 to 15 cm.) in diameter, appeared in the buttocks at the sites of injection of penicillin. Similar areas appeared on the chest and back at uninoculated sites, and one was found over the great trochanter of the left femur, where a subcutaneous injection of dihydromorphinone hydrochloride had been given. Fluctuation appeared in two of the indurated areas, and 3 cc. of thick, inodorous pus mixed with blood was aspirated from one.

No micro-organisms were found on direct smear or on aerobic or anaerobic culture of the pus, and dark field examination did not reveal the presence of spirochetes. A white cell count performed on February 25 showed 29,600 leukocytes per cubic millimeter of blood, of which 93 per cent were of the polymorphonuclear series. A culture of the blood at the height of the febrile reaction was sterile, and cultures of material from the edematous throat tissue showed Micrococcus catarrhalis together with hemolytic and nonhemolytic streptococci. A culture of the dihydromorphinone hydrochloride used for subcutaneous injection was bacteriologically sterile, and other patients inoculated with the same preparation and penicillin solutions as were used on J. M. did not show any local or general reaction.

The appearance of the nodular ulcerative syphilid on the forearm was unchanged throughout the entire period of observation. It became necessary, after 1,000,000 units of penicillin had been given, to discontinue penicillin treatment, on February 25, owing to the development of incessant vomiting and slight delirium. Fever persisted until March 4, the temperature reaching a maximum of 104.6 F. on February 24 and remaining above 102 F. through February 28. Both pulse and respiration rates rose and fell with the temperature. All symptoms except slight soreness of the throat had disappeared when the patient was last seen, on March 7, 1945.

COMMENT

In view of the fact that nonsyphilitic persons were treated without reaction with the same solution of penicillin as was used on a person whose only detectable disease was syphilis, it is reasonable to assume

From the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine.

1. Mahoney, J. F.; Arnold, R. C.; Sterner, B. L.; Harris, A. D., and Zwally, M. R.: Penicillin Treatment of Early Syphilis, J. A. M. A. **126**:63 (Sept. 9) 1944.

2. Stokes, J. H.; Sternberg, T. H.; Schwartz, W. H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B.: The Action of Penicillin in Late Syphilis, J. A. M. A. **126**:73 (Sept. 9) 1944.

that the reaction sustained by that patient was due to the action of penicillin on Treponema pallidum. Consideration of the nature of the action can only be speculative and must be founded on the effect on the tissues of the products of destruction of the spirochete, such effect being brought about either directly, by a primary irritant, or indirectly, through an antigen-antibody reaction. The absence of reaction at the site of the gummatous lesions on the forearm can be interpreted on the basis of an assumption that the development of the lesion, two years prior to therapy with penicillin, had exhausted some or all of the materials essential to reaction with spirochetal products at that site.

ERYSIPELOID TREATED SUCCESSFULLY WITH INJECTIONS OF PENICILLIN

Report of a Case

MAURICE J. COSTELLO, M.D., NEW YORK

P. W., a white woman aged 66, was examined on July 10, 1945, because she complained of a papular urticarial eruption on the limbs which had been present for about five days. At this time she called attention to an eruption confined to the third finger of her right hand. She stated that on July 7 she cleaned a perch, and one of the sharp scales became embedded in her finger. The finger presented a mottled red appearance. It was swollen and shiny and painful to pressure. There were pain and stiffness when the finger was flexed. The portal of entry of the infection was at about the middle of the medial aspect of the finger, where there was a whitish spicule embedded in the skin. The patient's temperature was 100.2 F. She was advised to apply wet compresses and to return to the office in one week.

On July 17, 1945, the condition had become worse, and it was decided to hospitalize the patient. She was admitted to St. Clare's hospital, where she was given 40,000 units of penicillin by intramuscular injection, at 8:00 and 11:00 a. m. and 2:00, 5:00 and 8:00 p. m. daily, until she had received 1,800,000 units over a period of nine days. On July 27 there was complete involution of the eruption with disappearance of the swelling and pain, and the skin began to exfoliate. On July 30 there was slight residual redness at the dorsal surface of the last phalanx, but the patient was apparently cured. It is believed that the response could have been even more rapid if the patient had received eight similar injections daily, rather than five, but the patient's age and infirmity had to be considered.

Correspondence

SEMBLANCE OF ELASTIC TISSUE TO MYCELIUM IN POTASSIUM HYDROXIDE PREPARATIONS

To the Editor:—I have read with interest a clinical note entitled, "Semblance of Elastic Tissue to Mycelium in Potassium Hydroxide Preparations," by Walter S. Green and Maurice C. Shepard in the August issue of the Archives of Dermatology and Syphilology. I should like to call attention to the work of two American authors, Isaac R. Pels and S. Bayne-Jones, of Baltimore, who published in 1923 an article on exactly the same subject (Elastic Tissue Simulating Mycelial Filaments in Skin Scrapings, Arch. Dermat. & Syph. **8**:37 [July] 1923). These authors stated that elastic tissue fibers in scrapings from lesions of the skin may so closely resemble the mycelial filaments of fungi as to lead to an error in diagnosis and the consequent use of inappropriate treatment. Their specimens, taken from granulomatous lesions and examined in potassium hydroxide, contained filaments which were mistaken for fungous mycelium by a number of competent observers. The filaments were delicate, long and hyaline, from 1.5 to 5 microns in diameter, with irregular width and apparently doubly contoured edges. The internal structure was glassy and almost free from granules. Some of the fibrils branched irregularly; others contained transverse striations which suggested septums. The ends of the fibrils were either blunt or tapering or were split longitudinally into a few smaller fibrils. The ends were often spirally curled. Along the sides of some of the fibrils were small prominences suggesting budding. All attempts to culture a fungus from the material containing these fibrils failed. Their peculiarities—the glassy nature and the curling and splitting ends—suggested the elastic tissue origin, which was finally proved by staining with Weigert's elastic tissue stain. The fibrils appeared dark purple or almost black with homogeneous structure.

C. Bruhns and A. Alexander (in Jadassohn, J.: "Handbuch der Haut- und Geschlechtskrankheiten," Berlin, Julius Springer, 1928, vol. 11, p. 89) mentioned the elastic fibers as the number one cause of mistakes in examination of skin scrapings for fungi. They are found often when the material consists not of superficial scrapings but of bits of deeper tissues in cases of granulomatous or ulcerated lesions. According to these authors, the elastic fibers never divide dichotomously and therefore can easily be distinguished from fungous filaments, which show such a division. It seems to me, however, that this remark will be of little help, because the true fungous filaments often show an irregular division. I believe that the most important diagnostic feature of fungous filaments will be their distinct septation and their tendency to break into chains of spores.

The technic of taking material for examination has much to do with the presence of elastic fibers in the preparation. As they are a normal constituent part of the corium, it is natural to obtain them if bits of tissue are taken from the deep inflammatory or ulcerated lesions extending into the corium. The common fungous diseases of the skin are superficial. The fungi are present only in the cornified layers of the epidermis. There is no need for penetrating into the corium with instruments. This, however, is difficult to avoid if a sharp scalpel is used to take shavings of skin. By using a not very sharp curet and taking scrapings rather than shavings, one can confine the action to the epidermis and thus avoid the presence of elastic fibers in the preparations.

It seems to me that these fibers cannot be called an "artefact." This term can properly be used in relation to structures artificially produced by laboratory procedures, for instance, air bubbles, oil droplets, granules of cellular detritus, crystals of potassium hydroxide, etc. The elastic fibers are a normal part of the skin and are no more an artefact than are epidermal cells or leukocytes.

E. Muskatblit, M.D., New York.

55 West Forty-Second Street.

To the Editor:—In the August issue of the Archives (**52**:115, 1945) under the title of "Semblance of Elastic Tissue to Mycelium in Potassium Hydroxide Preparations," Drs. W. S. Green and M. C. Shepard call attention to a condition which was described some time ago by Dr. S. Bayne-Jones and me (Elastic Tissue Simulating Mycelial Filaments in Skin Scrapings, Arch. Dermat. & Syph. **8**:37-43 [July] 1923). Our article was based on a study of 2 cases of granulomas of undetermined origin.

In the light of these publications it should be stated that open or eroded areas examined for fungi should be suspected of revealing elastic tissue which may simulate mycelial filaments. It is of course timely to reiterate this concept in view of the importance of establishing a diagnosis.

We could find no mention of this experience in the literature preceding our publication.

Isaac R. Pels, M.D., Baltimore.

DEMONSTRATION OF EFFECT OF NUTRITION ON THE SKIN

To the Editor:—Because there are differences of opinion with regard to the effect of nutrition on the skin, the following record of prolonged observation is offered for your consideration.

About 1890 the Lanette, Ala., cotton mills were built on the farm on which I was born and a cottonseed oil press operated nearby. Housewives gathered around a demonstration of the use of this oil in cooking. In 1896, as a freshman who preferred books to meat, I went on a Hindhede diet (chiefly bread and milk) for three months. My skin became rough and irritable but cleared up after three months of eating fat meat and drinking oil. In 1912 I drank 1 ounce (28 cc.) of cottonseed oil every day for six months, with similar results.

In 1918, while I was serving with the Nutrition Division, United States Army, an exudative eczema developed that interfered with military duty. Allergy tests elicited negative reactions. Fat meat relieved the

eczema, whereas dairy products did not; in fact, sometimes a meal with much cream made it worse. Since the high fat diets were low in carbohydrate, I tried a diabetic diet for a year. This relieved the eczema but lowered my sugar tolerance, and when I returned to a normal diet furunculosis developed, of which I have had repeated attacks to the present time. The lowered sugar tolerance was not accompanied with glycosuria, even after I had taken 250 Gm. of glucose, but there was a delay in return of the blood sugar to normal. With insulin, I could reduce my blood sugar to 37 mg. per hundred cubic centimeters without losing consciousness.

In 1930, after reading the papers of Urbach and collaborators, I became interested in the sugar and water contents of the skin and made determinations on the skin of rats fed various diets. Urbach now calls the condition "skin diabetes." From a dietary standpoint, however, there seems to be a distinction between the diet relieving eczema and that relieving furunculosis.

Furunculosis is relieved by reducing the rapidly absorbed carbohydrates (replacing them with any fat). But, as Burr and Burr first showed with rats and Arild Hansen with children, eczema is relieved only by linolic and arachidonic acids.

There was always a return of eczema on stopping use of the essential fatty acids, and I have purposely let it return at least once every five years. Since 1930 I have drunk 5 gallons (187 liters) each of corn, cottonseed and raw linseed oils and eaten 40 pounds (18 Kg.) of lard to control eczema.

In 1932, in a paper in the Tokyo Izi Sinsi (no. 2907), I attributed the effect of linolic and arachidonic acids to the formation of their choline-glycerophosphate and cholesterol esters, which waterproofed the epidermal cells of the skin. This was based on electrical resistance and chemical studies of the cells and on the fact that eczema (especially the itching) was made worse by the passage of water through the skin due to alternate wetting and drying.

J. F. McCLENDON,
Lt. Col., U. S. Army Reserve, Nutrition Div.
Hahnemann Medical College, Philadelphia.

Obituaries

KENDAL FROST, M.D.
1890-1945

Kendal Frost, son of Dr. Fred R. Frost and Mary Humphreys Green, was born Nov. 9, 1890, in Los Angeles. After graduating from a private boys' school, he attended the University of California and obtained a B.L. degree in 1913 and an M.D. degree in 1914. He then went to Rush Medical College, and his M.D. degree was conferred on him in 1916. After that he served an internship at the Presbyterian Hospital in Chicago where he came under the tutelage of Dr. Ormsby, of whom he remained a life-long admirer and devoted friend. He was attached for eleven months to the British Expeditionary Forces during World War I, later recalled to the American Forces. Altogether he spent twenty-four months overseas. After the armistice he was with the Belgian Relief Commission.

At the time of his death he was a member of the American Medical Association; American Dermatological Association; American Academy of Dermatology and Syphilology, Inc.; Los Angeles Dermatological Society; Los Angeles Academy of Medicine; American College of Physicians; Los Angeles Symposium Society; Los Angeles Museum Patrons Association; California Club, and Theta Delta Chi Fraternity.

Dr. Frost was a diligent worker; aside from a yearly vacation his time was largely taken up

KENDAL FROST, M.D.
1890-1945

with dermatologic activities. He had a busy office practice, occupied the chair of dermatology at the University of Southern California and was in charge of the dermatologic work at the Good Hope Clinic. For many years he was consultant in dermatology to the Santa Fe Coast Lines Hospital and was also on the staff of St. Vincent's Hospital and Hospital of the Good Samaritan. He was one of the founders of the Los Angeles Dermatological Society and remained an active and interested participant in its meetings until his health no longer permitted it. His thinking was always basic and sound, and therefore his participation in the societies' meetings will be sorely missed by his colleagues. He was never the first to accept the new or the last to discard the old. Personal exhibitionism had no part in his program.

Dr. Frost formed a limited number of friendships, and to these friends he remained warmly devoted. His tastes were refined; he was much interested in various musical activities in Los Angeles and was an accomplished pianist. His collection of artistic prints, which he selected himself, are a valuable possession. His social activities were largely carried on in intimate association with his family. Dr. Frost was a native son of California and, while he said little about it, was proud of it. While still comparatively young at the time of his death, he must be looked on as one of the pioneers of modern dermatology in Southern California. He leaves a widow, Mrs. Dorothy Frost, a son, Kendal Jr., and a daughter, Rebecca. He died Sept. 27, 1945, after a long illness.

WILLIAM H. GOECKERMAN, M.D.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

GENERALIZED VACCINIA IN AN ECZEMATOUS CHILD: DEMONSTRATION OF VIRUS AND COMMENT ON "KAPOSI'S VARICELLIFORM ERUPTION." FALLS B. HERSHEY and WILLIAM E. SMITH, Am. J. Dis. Child. **69**:33 (Jan.) 1945.

In this communication from the department of pediatrics and of pathology of the Massachusetts General Hospital, a case is reported of generalized vaccinia occurring in an eczematous child after exposure to a recently vaccinated brother. The vaccine virus was recovered from the cutaneous lesions, and antibodies against this virus were demonstrated in the serum of the patient. The cutaneous lesions of the vaccinia developed almost exclusively in the eczematous areas.

Recently, agents closely resembling herpes simplex virus have been recovered from similar eruptions known as Kaposi's varicelliform eruption or pustulosis variioliformis acuta. Since these eruptions occur in patients with eczema, they were formerly considered to be identical with eczema vaccinatum. However, a considerable number of patients have failed to yield either vaccinia or herpes virus despite appropriate tests. The suggestion is made that this may be due to other viruses localizing in the eczematous areas.

ACUTE GLOMERULAR NEPHRITIS IN AN INFANT WITH CONGENITAL SYPHILIS. JOSEPH YAMPOLSKY and DEWITT F. MULLINS JR., Am. J. Dis. Child. **69**:163 (March) 1945.

The authors report a case of acute glomerular nephritis in an infant with congenital syphilis. The observations at autopsy are given. The literature on the causation and diagnosis of hemorrhagic nephritis in the newborn is reviewed. While the authors' patient had congenital syphilis, it is not at all certain that this disease was the cause of the nephritis.

NELSON PAUL ANDERSON, Los Angeles.

SARCOIDOSIS OF BOECK: METABOLIC STUDIES OF 3 CASES. B. M. STUART, Am. J. M. Sc. **208**:717 (Dec.) 1944.

From extensive studies of 3 patients with sarcoidosis (2 of whom had the uveoparotid syndrome) Stuart found that serum alkaline phosphatase values were elevated while acid phosphatase values were normal. The results of other laboratory procedures merely confirmed the observations of other authors.

LYNCH, St. Paul.

ABDOMINAL ANEURYSMS. VIRGIL SCOTT, Am. J. Syph., Gonor. & Ven. Dis. **28**:682 (Nov.) 1944.

In 96 patients the presence of abdominal aneurysms was proved by autopsy, by exploratory laparotomy or on the basis of clinical and roentgenologic observations. The cause of the abdominal aneurysms (aorta and branches) in these 96 patients was as follows: syphilis, 58.3 per cent; arteriosclerosis, 20 per cent; bacterial agents 18.8 per cent; periarteritis nodosa, 1 per cent, and tuberculosis, 1 per cent. Multiple abdominal aneurysms were present in 18.7 per cent of the patients. The incidence of syphilitic aneurysm was highest in the Negro race (42 per cent) and in the male sex (84 per cent).

The symptomatology of abdominal aneurysm is variable because of the differences in location and size. In the syphilitic group the most significant symptom was pain in the abdomen or back which was present in 84 per cent of the patients. This pain was most severe at night and was relieved by a change of position. A mass exhibiting an expansible pulsation, a palpable thrill and an audible bruit is the most characteristic physical manifestation of abdominal aneurysm. The important roentgenologic changes observed are erosion of the vertebral column resulting from pressure of the aneurysm and the presence of calcium deposits in the wall of the aneurysmal mass. The prognosis is usually grave.

SYSTEMIC MANIFESTATIONS OF BISMUTH TOXICITY. ALBERT HEYMAN, Am. J. Syph., Gonor. & Ven. Dis. **28**:721 (Nov.) 1944.

Four patients with severe systemic manifestations and renal insufficiency following bismuth therapy are reported on. Two died. The other 2 had severe bismuth melanosis of the large intestine and cervicovaginitis due to bismuth. The role of bismuth in the production of renal insufficiency is discussed, and the relation of previous renal damage to bismuth toxicity is emphasized. Caution is advised in the use of bismuth in treatment of patients with previous renal damage.

PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS RESISTANT TO ARSENIC AND BISMUTH. R. A. NELSON and L. DUNCAN, Am. J. Syph., Gonor. & Ven. Dis. **29**:1 (Jan.) 1945.

Six patients with early syphilis resistant to arsenic-bismuth chemotherapy were treated with penicillin. The cutaneous lesions in all the patients were of the psoriasiform type, and spirochetes could be demonstrated in the material from the lesions of 5 of the 6 patients. Varying dosage schedules were employed, ranging from a total dose of 60,000 to 2,000,000 Oxford units, although on the basis of available information to date the authors would administer 2,400,000 units of penicillin intramuscularly in sixty injections of 40,000 units each, given every three to four hours around the clock.

Penicillin was uniformly successful in destroying surface spirochetes and in healing lesions in all the patients. In some 2,000 patients with early syphilis so far treated with penicillin, no examples of penicillin-resistant syphilis have been as yet encountered.

INFECTIVITY OF HEMOPHILUS DECREYI FOR THE RABBIT AND THE DEVELOPMENT OF SKIN HYPERSENSITIVITY. R. R. FEINER and FRANCO MORTARA, Am. J. Syph., Gonor. & Ven. Dis. **29**:71 (Jan.) 1945.

Lesions were produced in the skin of rabbits by intradermal or multipressure inoculation of living virulent cultures of Hemophilus Ducreyi. Injection by other routes or with heat-killed organisms was without effect. H. Ducreyi could be isolated in pure culture from

lesions of rabbits, and from such cultures lesions in new animals could be reproduced and organisms again recovered.

A cutaneous hypersensitivity to H. Ducreyi vaccine developed after the production of a cutaneous lesion by intradermal injection of virulent organisms. This hypersensitivity lasted at least three months. No hypersensitivity developed after repeated intradermal injections of the vaccine itself or the injection of living organisms by other routes.

AN EXPERIMENTAL INVESTIGATION OF THE ETIOLOGY AND IMMUNOLOGY OF GRANULOMA INGUINALE. KATHERINE ANDERSON, W. A. DEMONBREUN and E. W. GOODPASTURE, Am. J. Syph., Gonor. & Ven. Dis. **29**:165 (March) 1945.

A micro-organism morphologically identical with the Donovan body of granuloma inguinale and its unencapsulated bacillary forms has been isolated and serially cultivated in the yolk of developing chick embryos. The same micro-organism has been isolated from the lesions of 3 patients with granuloma inguinale. Embryonic yolk in vitro supports the growth of the micro-organism. Washed bacterial bodies stimulate an apparently specific cutaneous reaction in the skin of patients with active granuloma inguinale.

A "capsular" substance which is precipitable from infected embryonic yolk gives an apparently specific precipitation reaction in patient's serum.

SOBISMINOL MASS IN THE TREATMENT OF SYPHILIS. CHARLES W. BARNETT and WILLARD M. MEININGER, Am. J. Syph., Gonor. & Ven. Dis. **29**:174 (March) 1945.

The authors report their further experience with sobisminol mass in the treatment of syphilis, some five years after their original report in 1939.

Ninety-three patients with early syphilis were treated with sobisminol mass in combination with neoarsphenamine or oxophenarsine hydrochloride. Fifteen patients showed clinical or serologic relapses, an incidence of 16 per cent. The high incidence of relapse was attributed to the type and the irregularity of treatment and the administration of sobisminol mass before use of the arsenicals was started.

In patients with late syphilis sobisminol mass produced a rapid involution of gummatous lesions, and a number of patients with advanced cardiovascular involvement and neurosyphilis were improved symptomatically. The toxicity of the drug is low, but about one third of the patients taking it experienced mild gastrointestinal disturbances. Indications for the use of sobisminol mass are discussed and its superiority to other substances used in antisyphilitic therapy under certain circumstances is pointed out.

THE CHEMOTHERAPY OF SYPHILIS. JOSEPH. E. MOORE, Am. J. Syph., Gonor. & Ven. Dis. **29**:185 (March) 1945.

This is an excellent article which reviews the chemotherapy of syphilis from the first appearance of the disease in Europe, in 1493, until October 1944. The last half of the article is devoted to the use of penicillin in treatment of syphilis, but since the picture regarding penicillin is changing so rapidly, details regarding its use are omitted from this abstract, except the statement that penicillin is a new and powerful addition to syphilotherapy.

REUTER, Milwaukee.

SYPHILIS: REVIEW OF THE RECENT LITERATURE. GURNEY CLARK, JOSEPH EARLE MOORE, CHARLES MOHR, VIRGIL SCOTT and RICHARD D. HAHN, Arch. Int. Med. **74**:390 (Nov.) 1944.

Mohr and his associates have again provided an extensive, thorough and critical review of literature pertinent to syphilis. The present review covers the period from July 1943 to July 1944 and is divided into sections relating to various laboratory, public health, therapeutic and clinical phases of the disease.

SPOROTRICHOSIS IN NEW YORK STATE: REPORT OF TWENTY-SIX NEW CASES AND TABULATED DISCUSSION OF TWENTY-SIX PREVIOUS ONES. GEORGE M. LEIBY, MARION B. SULZBERGER and RUDOLF L. BAER, Arch. Int. Med. **75**:145 (March) 1945.

Leiby, Sulzberger and Baer tabulated data covering 26 cases of proved or presumptive sporotrichosis previously reported in the state of New York. They describe 2 additional cases, 1 of which was clinically typical and 1 atypical in localization and appearance, involving an upper eyelid. They believe that such atypical and rudimentary sporotrichosis may often escape diagnosis and that infections with sporotrichum fungi may be more common in the state of New York than is indicated by the number of published reports. They state that the intracutaneous test with sporotrichin is a valuable aid in early diagnosis and should be employed in all cases of suspected sporotrichosis, in addition to the usual cultures.

ESOPHAGEAL CARCINOMA IN BRITISH WEST INDIAN AND PANAMANIAN NEGROES: A STUDY OF THE INCIDENCE, ETIOLOGIC FACTORS AND PATHOLOGIC ANATOMY IN FIFTY CASES. WRAY J. TOMLINSON and LESTER A. WILSON JR., Arch. Path. **39**:75 (Feb.) 1945.

Carcinoma of the esophagus is common in the Negroes of the British West Indies. Among 50 patients, 25 had clinical and autopsy evidence of syphilis (1 had associated leukoplakia). The average incidence of syphilis was 8.7 per cent in the autopsy material under consideration.

LYNCH, St. Paul.

PROPIONATE AND UNDECYLENATE OINTMENTS IN THE TREATMENT OF TINEA PEDIS AND AN IN VITRO COMPARISON OF THEIR FUNGISTATIC AND ANTIBACTERIAL EFFECTS WITH OTHER OINTMENTS. EDMUND L. KEENEY, LIBERO AJELLO, EDWIN N. BROYLES and ELSIE LANKFORD, Bull. Johns Hopkins Hosp. **75**:417 (Dec.) 1944.

In an interesting study stimulated by the previous work of Peck and Hopkins, the authors record the clinical effectiveness of propionate–propionic acid ointment and of undecylenate–undecylenic acid ointment in the treatment of tinea pedis. They compared the in vitro fungistatic and antibacterial effects of the propionate–propionic acid ointment and of the 5 and 10 per cent undecylenate–undecylinic acid ointments with those of half and full strength ointments of benzoic and salicylic acid, 10 per cent ammoniated mercury, 5 per cent sulfathiazole and 0.5 per cent tyrothricin.

Tested in vitro on an especially resistant strain of Trichophyton gypseum, the propionate–propionic acid was superior to all the other ointments mentioned. The antibacterial effect on Staphylococcus aureus and on beta hemolytic streptococci was likewise greatest with the propionate–propionic acid ointment.

This ointment as well as undecylenate–undecylenic acid ointment does not produce irritation or sensitization in clinical use. Further, these ointments have the additional qualifications of fungistatic or fungicidal activity, antibacterial effect and penetration.

The authors feel that use of either of these fatty acid ointments in the treatment of tinea pedis is an improvement over any method of treatment in use at the present time.

NELSON PAUL ANDERSON, Los Angeles.

LUMBAR PUNCTURE HEADACHES. MYRON J. LEVIN, Bull. U. S. Army M. Dept., November 1944, no. 82, p. 107.

Lumbar spinal punctures were performed on 2,217 syphilitic candidates for induction into the armed forces. The fluids were collected rapidly; the patients immediately got up and were instructed to keep active and not to lie down. Only 15 cases of postpuncture headache were severe enough to require rest in bed were reported.

YAWS IN A WHITE SOLDIER. HAROLD RIFKIN, Bull. U. S. Army M. Dept., March 1945, no. 86, p. 81.

The patient was a 29 year old white soldier who had been on duty for one year in various islands in the South Pacific on which natives are known to have yaws. Two months prior to his admission to the hospital he had "stuck a splinter in the middle finger of his right hand," and thereafter an ulcer developed at the site. The soldier had played with native children but denied that he had had sexual contact during the entire stay in this area. On admission to the hospital he had an ulcer 12 mm. in diameter on the volar aspect of the distal phalanx of the middle finger of the right hand and a maculopapular eruption on the palms, soles, chest and abdomen. A dark field examination of the ulcer revealed an occasional spirochete, and spirochetes resembling Treponema pertenue were found in sections of skin and lymph nodes. The Kahn reaction of the blood was reported as 4 plus positive.

The patient was given oxophenarsine hydrochloride twice a week and a bismuth preparation once a week. After the third injection of the arsenical the Kahn reaction became negative and the ulcer was healing. The ulcer was healed after the fifth injection of oxophenarsine hydrochloride. The patient was given a total of eleven injections of oxophenarsine hydrochloride and three of the bismuth drug. The enlargement of lymph nodes was gone at the completion of this course of therapy; the cutaneous lesions had undergone involution, and the Wassermann reaction was still negative three months later.

TREATMENT OF YAWS WITH PENICILLIN. RICHARD WHITEHILL and ROBERT AUSTRIAN, Bull. U. S. Army M. Dept., March 1945, no. 86, p. 84.

The authors treated 17 patients with primary and secondary yaws from which Treponema pertenue was isolated by dark field examination. Most of the patients were given a total of 400,000 to 500,000 units of penicillin over a period of five days. The organisms disappeared from the cutaneous lesions within sixteen hours in 16 cases and within forty hours in 1 case.

Penicillin therapy brought about complete healing within three weeks of all the cutaneous manifestations of yaws, with the exception of one lesion which failed to epithelize because of local scar formation.

During the short period of observation penicillin did not affect significantly the Kahn reaction of the serum in yaws.

STRAKOSCH, Denver.

RUBELLA AND CONGENITAL MALFORMATIONS. EDITORIAL, Internat. M. Digest **46**:50 (Jan.) 1945.

In this editorial, attention is called to several reports in the literature of congenital malformations occurring in infants born of mothers who had rubella during pregnancy. The malformations are serious, occurring usually in the form of cardiac lesions or ocular lesions, particularly congenital glaucoma with resulting blindness. There have been relatively few published reports, but a number of cases have been observed, and they indicate that the incidence of malformations is close to 100 per cent when the rubella occurs in the early months of pregnancy. The question is raised as to the justification of therapeutic abortions in such cases or in any case of virus disease occurring early in pregnancy.

RATTNER, Chicago.

RECENT TRENDS OF LEPROSY IN THE UNITED STATES. RALPH HOPKINS and G. H. FAGET, J. A. M. A. **126**: 937 (Dec. 9) 1944.

During the last fifteen years 723 patients have been studied in the National Leprosarium. Serologic tests were of little value in the differentiation of leprosy from syphilis but were of some value as an index of the prognosis and of the progress of leprosy. Promin (p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate) and diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) proved to be the most beneficial of the numerous experimental drugs investigated. Nephritis and tuberculosis were the direct cause of almost half of the 190 fatalities.

HODGKIN'S DISEASE. S. R. BERSACK, J. A. M. A. **126**: 1025 (Dec. 16) 1944.

Bersack reports a case of Hodgkin's disease of the skin with terminal spread through the blood stream. The absence of any evidence of dissemination of embolic cellular element is consistent with a virus causation of Hodgkin's disease.

OCCUPATIONAL DERMATITIS CAUSED BY GERMICIDAL POWDER "MICROLENE." ALEXANDER STERLING, J. A. M. A. **127**:219 (Jan. 27) 1945.

A severe dermatitis of four years' duration involving hands and forearms occurred in a waitress from indirect contact with a germicidal chemical powder, Microlene, used in a dishwashing machine. A patch test with Microlene elicited a strongly positive reaction.

TREATMENT OF VINCENT'S ANGINA WITH SULFATHIAZOLE. WILLIAM W. MANSON and IRWIN T. CRAIG, J. A. M. A. **127**:277 (Feb. 3) 1945.

A total of 48 patients with Vincent's angina were treated with sulfathiazole, without recurrences. The treatment consisted of 1 sulfathiazole tablet (0.5 Gm.) dissolved on the tongue every two hours during the day and 2 such tablets dissolved in the same manner every four hours at night. The treatment was continued for a total of seventy-two hours.

SKIN-HAZARDS IN MANUFACTURE AND PROCESSING OF SYNTHETIC RUBBER. LOUIS SCHWARTZ, J. A. M. A. **127**:389 (Feb. 17) 1945.

Comparatively little dermatitis occurs in persons engaged in the manufacture of synthetic rubber. Workers in this industry take a shower bath immediately after

completing the job, then remove protective clothing and don their street clothes.

OVERTREATMENT DERMATITIS. L. E. GAUL, J. A. M. A. **127**:439 (Feb. 24) 1945.

When the routine dermatologic history of a patient is taken, the previous treatment is recorded in sequence. Patch tests are performed with previously tried medicaments as well as with other suspected contactants. During the interim compresses of sodium chloride solution or a colloidal clay lotion or paste is applied. The post-treatment patch test reduces the incidence of overtreatment dermatitis.

PENICILLIN IN THE TREATMENT OF INFANTILE CONGENITAL SYPHILIS. R. V. PLATOU, ALLEN J. HILL, NORMAN R. INGRAHAM, MARY S. GOODWIN, ERLE E. WILKINSON and ARILD E. HANSEN, J. A. M. A. **127**:582 (March 10) 1945.

Sixty-nine infants with manifest early congenital syphilis were treated with sodium penicillin. Penicillin was administered intramuscularly in isotonic solution of sodium chloride every three hours in sixty injections over a seven and one-half day period. Total doses used ranged from 16,000 to 32,000 Oxford units per kilogram of body weight. Three infants died during or soon after treatment. All of these had active syphilitic lesions, were under 2 months of age and were in poor general condition. Thirty-nine infants were followed from four to twelve months. Twenty-five of these now are physically normal and have doubtful or negative serologic reactions (21 negative and 4 doubtful). Serologic relapse occurred in 5 infants and clinical relapse in 2 of these 5. The results obtained in this series were not entirely satisfactory. Accordingly, the authors recommend temporarily a total dose of 40,000 Oxford units per kilogram of body weight, given in sixty intramuscular injections over a seven and one-half day period.

STATUS OF POISON IVY EXTRACTS. F. A. STEVENS, J. A. M. A. **127**:912 (April 7) 1945.

It is highly probable that urushiol is the irritant in poison ivy, sumac and the lac trees. Dermatitis venenata is the result of contact after previous exposure and sensitization to the active substance in the plants. Persons who show strongly positive cutaneous reactions with ivy extracts and who are susceptible to the dermatitis can be rendered dermally insensitive to the test and also resistant to rigorous exposure to the plants by the daily ingestion of large increasing doses of ivy extracts. These subjects are desensitized rather than immunized. Most are only temporarily "resistant" to or "protected" against ivy. So far none of the potent extracts for oral therapy have been marketed. There is no satisfactory evidence that the cutaneous reaction or the resistance to poison ivy on rigorous exposure has ever been modified, except by the aforementioned procedure, a procedure which its instigators imply is probably unsafe except under experienced supervision and probably not worth while because the resistance seems but temporary. There is clinical evidence that intramuscular inoculations have conferred resistance on susceptible persons. Since the cutaneous reaction has not been modified and the inoculated subjects have not been rigorously exposed under supervision, some doubt is cast on the validity of the evidence purporting to show protection afforded by intramuscular inoculation. The treatment of the acute rash with ivy extracts should be discouraged because many patients are made worse and there is no satisfactory evidence that any are helped.

"DIAPER RASH" DUE TO PERM-ASEPTIC. WILLIAM J. DOBES, J. A. M. A. **128**:281 (May 26) 1945.

Five cases of diaper rash caused caused by Perm-Aseptic are reported. It is used in the last rinse by diaper services. The purpose is to make textiles active antiseptic as a protection to persons and as a preventive of destruction of textiles by bacteria, germs, mold and mildew. Patients wore the diapers treated with Perm-Aseptic for at least two months before symptoms of sensitivity appeared.

HENSCHEL, Denver.

THE SPIROCHETICIDAL ACTION OF PENICILLIN IN VITRO AND ITS TEMPERATURE COEFFICIENT. HARRY EAGLE and ARLYNE D. MUSSELMAN, J. Exper. Med. **80**:49 (Dec.) 1944.

Experiments were performed in an attempt to demonstrate the mode of action of penicillin in the treatment of syphilis. Penicillin was found to be actively spirocheticidal in vitro against several strains of nonpathogenic Treponema pallidum. Although rendered non-viable, the organisms remained motile for eight to twenty-four hours. The rate of killing by penicillin increased with temperature in the range 8 to 40 C.

THE ROLE OF THE LYMPHOCYTE IN ANTIBODY FORMATION. T. N. HARRIS, E. GRIMM, E. MERTENS and W. E. EHRICH, J. Exper. Med. **81**:73 (Jan.) 1945.

Previous observations by two of the authors had suggested that the lymphocyte may play an important role in antibody formation. The present report deals with confirmatory observations.

LYNCH, St. Paul.

THE EFFECT OF TUBERCULOUS AND SENSITIZED SERA AND SERUM FRACTIONS ON THE DEVELOPMENT OF TUBERCLES IN THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK. EMILY W. EMMART and FLORENCE B. SEIBERT, J. Immunol. **50**:143 (March) 1945.

The authors made electrophoretic analyses of the amount of albumin and alpha, beta and gamma globulins present in tuberculous, "sensitized," and normal rabbit serums. They then implanted these whole serums simultaneously with tubercle bacilli of the A 27 strain on the chorioallantoic membranes of 8 day old chick embryos. The incidence of membranes in which tubercles developed was calculated and the size and development of the tubercles noted. Under these experimental conditions, serums either from rabbits sensitized with a purified tuberculin protein preparation or from tuberculous rabbits possessed tuberculostatic activities in the chick membrane. Both types of serums had higher gamma globulin contents than serums from normal rabbits. Serums from sensitized rabbits implanted on the chick membrane the day before inoculation with tubercle bacilli also produced partial inhibition of the development of the tubercles in the chick membrane. A gamma globulin fraction isolated from pooled "sensitized" rabbit serums caused partial inhibition of tubercle development while the remaining protein fraction did not. There was a suggestion of partial tuberculostatic effect due to a gamma globulin fraction isolated from pooled serums of patients with minimal tuberculosis, although the data were insufficient to be statistically significant.

ACTERIAL DESTRUCTION OF NICOTINIC ACID. STEWART KOSER and GRACE ROSSKOFF BAIRD, J. Infect. Dis. **75**:250 (Nov.-Dec.) 1944.

Little is known about the capacity of bacteria to accomplish the destruction of vitamins. Most microbiologic work dealing with accessory factors has been concerned with the nutritive requirements of various bacteria, yeasts or higher fungi, with the use of microorganisms for vitamin assay procedures or, more rarely, with their use as "tools" to study the function of vitamins. In the present investigation, the authors studied the decomposition of nicotinic acid, paying particular attention to the bacteria capable of growing in a medium containing this vitamin as the only organic compound.

They found that bacteria of the green fluorescent pigment-producing group, Pseudomonas fluorescens and allied types, and also Serratia marcescens and related species are able to grow in a simple synthetic medium containing nicotinic acid as the only organic compound. Low concentrations of nicotinic acid support growth while amounts of from 0.5 to 1 per cent often delay growth or inhibit it entirely. Destruction of nicotinic acid, as measured by the chemical method, occurs during cell multiplication. When 0.1 per cent nicotinic acid is supplied, often 95 per cent or more of the vitamin is utilized; in the presence of 0.5 per cent nicotinic acid, a smaller proportion of the total amount is destroyed.

Many cultures fail to grow or grow but poorly when nicotinamide is substituted for the acid. All cultures fail to grow when the isomers isonicotinic and picolinic acids are supplied in place of nicotinic acid. Several other derivatives are utilized less readily than nicotinic acid. Both groups of bacteria causing the breakdown of nicotinic acid also synthesize the vitamin when grown in mediums originally devoid of it. The results emphasize the broader field of destruction of vitamins by bacteria, in contrast to the better recognized role of vitamins as coenzymes or accessory factors.

NOTE BY ABSTRACTER.—Nicotinic acid is found in sweat. The subject matter discussed here should furnish a lead for investigating the action of fungi imperfecti on sweat and the possibilities for the use of this information in therapeutic measures.

THE INFECTION OF TICKS (DERMACENTOR VARIABILIS) WITH PASTEURELLA TULARENSIS. J. FREDERICK BELL, J. Infect. Dis. **76**:83 (March-April) 1945.

Present methods for the control of tularemia are not founded on an understanding of the ecology of the disease. In this study an attempt, based principally on analogy with the results of similar studies on plague, was made to determine the nature of the barriers to the spread of tularemia among ticks. Individual variations in susceptibility to infection was a possible cause of lack of uniformity of infection in ticks of an exposed group, and it is suggested that increased susceptibility to infection might result from decreased vitality, but the subject was not carefully investigated. Bacteriophage was not discovered in any of the experiments.

In the few samples tested the fecundity of infected ticks, as measured by the production and fertility of ova, was not diminished, nor was viability adversely affected.

The data indicate that the epizootic course of tularemia does not depend merely on a large number of ticks and the presence of many suitable hosts, and "hereditary" transmission does not appear to be of significance for Dermacentor variabilis, as no evidence of infection thus transmitted was obtained. "Hereditary" transmissions, therefore, may be the exception rather than the rule in nature, and the lack of it would be a most important limiting factor.

That 1 rabbit that was fed on by several hundred infected ticks did not die or even become ill of tularemia was ascribed to the fact that the animal had previously been fed on by ticks and probably had developed an immunity to the parasite which acted in a nonspecific way (probably through a cellular mechanism) to prevent infection.

The author demonstrated that infected ticks feeding on immune or normal hosts lose their infection, presumably as a result of the stimulating effect of the blood meal in a normal bactericidal function of the tick's gut, but, before losing their infection as a result of feeding, infected ticks may inoculate the host, whereupon the host, if it is not immune, will acquire septicemia and infect all ticks feeding on it. Infected ticks feeding on immune hosts, on the other hand, permanently lost their infections and the bacteria were not transmitted to normal ticks feeding concurrently.

Since the blood meal causes eradication of infection already present in ticks, Bell advances the theory that organisms acquired by feeding on the blood of animals with septicemia are not also destroyed because a factor is present in normal blood which is complementary to and necessary for the action of the bactericidal element resident in the tick; he further supposes that septicemia removes this hypothetic factor from the blood, thus permitting invasion of the ticks by the organisms. The importance of immune animals in limiting the spread of tularemia is indicated by these experiments. The feeding of ticks was greatly facilitated by heightened temperature of the environment. The enhancement of the normal bactericidal principle present in ticks at high temperatures, according to the law of Vant Hoff, could not be demonstrated in regard to the survival of infecting bacteria in nymphs of D. variabilis.

CORNBLEET, Chicago.

ALLERGY FROM TIMBÓ (LONCHOCARPUS H.B.K.). A. OLIVERIA LIMA, J. Lab. & Clin. Med. **29**:939 (Sept.) 1944.

This is a report of the case of a Brazilian man in whom after exposure to an insecticide and to flora of the Amazon region, asthma and a dermatitis of the contact type developed. He became allergic at the same time to the atopenic and resinous principles of timbó. The author was able to demonstrate by a series of scratch, intradermal and patch tests that the patient was sensitive to both timbó and Derris (cubé). The atopenic and contact principles of the two genera belong to two different classes of substances: The timbó belongs to the genus Lonchocarpus and derris to the Leguminosae family. The eczematous eruptions occurred only when the crude extracts of the Lonchocarpus and derris leaves were used. The eruption did not appear when the resinous principle of leaves and roots of the plants were extracted with ether. On studying the antigenic behavior of the atopenic principle of the two genera by means of Dale test (sensitized uterine strips), the author was able to demonstrate an immunologic relationship between the water-soluble antigens of timbó and derris.

AN ALKALINE MEDIUM AND PROCEDURE FOR THE SELECTION OF DERMATOPHYTES IN THE PRESENCE OF SAPROPHYTIC FUNGI. J. M. LEISE and L. H. JONES, J. Lab. & Clin. Med. **30**:119 (Feb.) 1945.

The purpose of this study is the selection of a medium of proper p_H in which pathogenic fungi (dermatophytes) could grow and be identified by suppressing the growth of the more rapidly growing saprophytic fungi.

In this study the authors found that in the growing of a mixed suspension of dermatophytes and saprophytic fungi the best results were obtained when they used poured plates of alkaline medium of Sabouraud's maltose agar of p_H 10.5 incubated five and one-half days at 34 C. Under these conditions, the inhibition of the saprophytic growth was greater than the inhibition of dermatophytes. A fluctuating room temperature was found to be more inhibitory for the dermatophytes.

There was an overgrowth of saprophytes in cultures over five and one-half days old. Plates which were negative for pathogenic fungi after the five and one-half days were further incubated for about ten days, with daily observation. Colonies that were thought to be pathogenic were transferred to suitable mediums for purification and examination.

The authors think that the effectiveness of the alkaline medium in selecting dermatophytes when in the presence of saprophytic fungi may be due to the presence of a trypsin-like enzyme system in the dermatophytes. The presence of such an enzyme system and the resultant ability to grow in highly alkaline substrates may be a characteristic of pathogenic fungi and bacteria and of pathogenicity itself.

The alkaline medium and culturing procedure may be used in the isolation of dermatophytes from infected skin, worn shoes and floors.

The historical review incorporated in this study is extensive and comprehensive.

GELBER, Los Angeles.

DERMATOLOGIC DISEASES FREQUENTLY ENCOUNTERED BY OTOLARYNGOLOGISTS. A. B. CANNON, New York State J. Med. **44**:1661, 1944.

Cannon discusses various forms of stomatitis and cheilitis resulting from dentifrices, lipstick, self biting and licking, phenolphthalein or other laxatives, vitamin deficiencies, leukoplakia, lichen planus, carcinoma, gumma and pemphigus. A brief outline of diagnosis and treatment is given.

EPITHELIAL CYSTS. F. A. DOLCE and R. L. CLARK, New York State J. Med. **44**:2358, 1944.

The authors describe 4 cases of epithelial cysts of the palms. The differential diagnosis between ganglions, fibromas and sebaceous cysts is discussed. Complete surgical removal is the treatment of choice.

THE WAR AND OXYGEN THERAPY. J. H. EVANS, New York State J. Med. **44**:2443, 1944.

After discussing oxygen therapy by inhalation, Evans describes subcutaneous oxygen therapy as being beneficial for local infections, arthritis in its acute stage, ringworm and burns, for relief of pain following dislocations and sprains and for promoting the healing of wounds. Mechanically it may act as follows: (1) opening up compressed lymph channels and providing better drainage; (2) serving as a buffer for inflamed tissues, thus relieving pain, and (3) improving local circulation of the blood. Evans reports that a few patients with ringworm were treated by subcutaneous oxygen therapy and that this method helped in the clearing up of bloody discharge and the healing of ulcerations.

INTENSIVE TREATMENT OF EARLY SYPHILIS-METHOD OF EAGLE AND HOGAN. G. M. MACKEE and G. [illegible] ASTRACHAN, New York State J. Med. **44**:2577, 1944.

The Eagle and Hogan method consists of tri-weekly injections of oxophenarsine hydrochloride for a total of six, eight or ten weeks, the dose being approximately 1 mg. per kilogram of body weight. Bismuth compounds may be given concurrently once a week. This treatment was given to 61 patients. Primary and secondary lesions healed in an average of twelve and six-tenths and seventeen and six-tenths days, respectively. In 58.8 per cent of the cases the serologic reactions were reversed completely to negative. The untoward reactions were in most of the cases of a mild character. The treatment had to be discontinued because of the severity of reactions in only 7 cases. This method is still in the experimental stage, and it should be used cautiously when one is dealing with cooperative patients.

CHICKENPOX, HERPES ZOSTER AND ACUTE ANTERIOR POLIOMYELITIS. J. C. MCGARRAHAN, New York State J. Med. **45**:193, 1945.

The author discusses the interrelationship between chickenpox and herpes zoster and presents a method of treatment (intravenous injection of thiamine hydrochloride) which was used in a case of chickenpox. It brought the disease to an abrupt end in six hours.

RONCHESE, Providence, R. I.

CHANCROID OF THE CERVIX. LOIS A. DAY, Proc. Staff Meet., Mayo Clin. **20**:70 (March 7) 1945.

Two cases of chancroid of the cervix are reported. In 1 of these cases the patient's husband acquired a chancroid in January 1944, while in the tropics, and was treated with a sulfonamide compound. His lesion rapidly underwent involution. He returned home in September, and five days later symptoms of chancroid developed in his wife. Examination of the husband did not reveal a lesion of the genitalia, and smears and cultures from the glans penis and prostatic cultures failed to demonstrate the presence of Hemophilus ducreyi. P. A. O'Leary, in discussing this case, states that the husband is a carrier of the organism, although its presence cannot be demonstrated. It has been known for some time that women may be carriers of H. ducreyi without demonstrable lesions, but it is rare that a man has been suspected of transmitting the disease in the absence of ulcerative lesions of the genitalia. Both patients responded to sulfathiazole administered by mouth and locally. In 1 of the patients intolerance to the sulfonamide drug developed, and penicillin was used advantageously. Zephiran chloride is the most efficient prophylactic agent against H. ducreyi.

HENSCHEL, Denver.

A CONTRIBUTION TO THE TREATMENT OF POST-IRRADIATION NECROSIS. JOHN E. MOSELEY, Radiology **44**: 262 (March) 1945.

The author reports 2 cases of radiation necrosis successfully treated with estrogenic ointment. Others to report good results in the treatment of radiation

...rosis with estrogenic hormones in oil are Sellers and Wagner. The rationale for such therapy is based on the fact that follicular hormones have a vasodilating effect on the smallest blood vessels of the skin and also have a selective growth-promoting action.

CIPOLLARO, New York.

VALUE OF SULFONATED OILS IN THE TREATMENT OF BURNS AND OTHER DENUDED SURFACES. WILLIAM L. ROGERS, THEODORE M. COHEN and RAYMOND R. GOLDBERG, U. S. Nav. M. Bull. **42**:1125 (May) 1944.

In cases of burns in which the initial shock is slight and facilities for primary débridement are available, the use of sulfonated oils was extremely effective for rapid cleansing of involved areas with negligible trauma. When a patient is in severe shock, the authors use a spray film preparation of the following formula:

	Gm. or Cc.
Paraffin wax	265
White wax	215
Sulfonated liquid petrolatum	330
Sodium lauryl sulfate	10
Water	30
A sulfonamide compound	50
Triethanolamine	100

The advantages claimed for this preparation are: (1) ease of application, (2) rapid removal of grease and dirt on subsequent washing, (3) chemotherapeutic agent available for absorption, (4) stimulation of granulating surfaces and (5) ability to treat large numbers of casualties quickly.

STUDIES ON FILARIASIS IN THE SAMOAN AREA. ELDON E. BYRD, LYLE S. ST. AMANT and LEON BROMBERG, U. S. Nav. M. Bull **44**:1 (Jan.) 1945.

Through laboratory and field studies convincing evidence was found that the mosquito Aedes scutellaris var. pseudocutellaris is the important transmitter of filariasis within the Samoan area. Since this species has a very short flight range, the authors suggest that military camps should never be quartered less than 500 yards (450 meters) from the nearest native habitation. Other precautions to be observed are: (1) complete isolation from native habitation; (2) prevention of natives from entering camp; (3) orders prohibiting troops from entering native villages during daylight, because of "day biting" habits of the mosquito hosts, and (4) the use of screened quarters and bed nets as standard items of equipment.

OUR LEPROSY PROBLEM. GEORGE M. SAUNDERS, U. S. Nav. M. Bull. **44**:54 (Jan.) 1945.

In a timely article, the author states that leprosy will soon become an American problem because an appreciable number of infections will develop among the troops who have served in endemic areas. He covers the subject thoroughly, discussing world distribution, etiology, clinical findings, diagnosis, treatment and prevention and control.

It is reemphasized that although there is no specific treatment for leprosy almost all patients show improvement with adequate diet, rest and suitable exercise. Other methods useful in controlling symptoms and complications are: (1) sulfonamide compounds for the treatment of secondary infections which complicate ulcerative lesions; (2) thiamine hydrochloride for relief from pain of neuritis; (3) surgical intervention to remove necrotic bones, and (4) tracheotomy for patients with laryngeal involvement.

SALT WATER ULCERS OF THE EXTREMITIES—OCCURRENCE IN JAPANESE SURVIVORS. CHARLES W. MCLAUGHLIN JR., and JAMES L. HOLLAND, U. S. Nav. M. Bull. **44**:494 (March) 1945.

An unusual type of ulcers on the extremities was observed in 13 Japanese survivors rescued in the South Pacific. These lesions in the early stages appeared as small vesicles or blisters, followed by gangrene and sloughing, leaving ulcers which varied from 0.5 to 3 cm. in diameter. The final lesions appeared as deep circular or oval punched-out ulcers with precipitous edges and a pinkish gray granulating base. The surrounding areas were free from any inflammatory reaction, but the edges were extremely sensitive. A temperature of 99 to 101 F., was invariably present when involvement was extensive. Repeated smears revealed gram-positive cocci in pairs and clumps. Healing was slow, and no difference in time was noted from the use of sulfonamide and other antiseptics and of dry sterile dressings.

The authors felt that these lesions were similar to the so-called "tropical ulcers" or "desert sores" and that trauma with exposure to salt water was the etiologic factor in the production of these ulcers.

GRANULOMA INGUINALE. JOHN G. MENVILLE, U. S. Nav. M. Bull. **44**:621 (March) 1945.

The author observed 4 cases of granuloma inguinale occurring in areas other than the inguinal region.

One atypical case is reported in which the disease began in a young Negro man as a penile lesion one week after sexual exposure. At the end of three weeks, the "pimple" enlarged into a rounded, button-shaped, flat, nontender red lesion, 2.5 cm. in diameter, located adjacent to the coronal sulcus and to the right of the frenulum.

Repeated dark field examinations and Kahn tests of the blood did not reveal syphilis. Microscopic examination of scrapings and a biopsy specimen were negative for leishmania bodies.

Treatment consisted of injection of 3 cc. of 1 per cent antimony and potassium tartrate intravenously the first day, the amount being increased 1 cc. each day until a total dose of 10 cc. was reached. The lesion showed improvement after the fourth injection and was completely healed in eighteen days.

RODIN, South Bend, Ind.

SKIN-ERUPTIONS DUE TO THE LOCAL APPLICATION OF SULPHONAMIDES. G. A. GRANT PETERKIN, Brit. J. Dermat. **57**:1 (Jan.-Feb.) 1945.

The author reports 65 cases of light eruption due to the external application of sulfonamide drugs. Thirty-two of the patients had been treated for impetigo; 8 for impetiginized seborrheic dermatitis; 3 for septic infection of the limbs; 2 for secondarily infected tinea of the feet; 5 for "running ears" (otitis externa), and 15 for wounds and burns of the limbs. In all but 4 cases the first sulfonamide drug to be applied was sulfanilamide powder. It is suggested that the eruption is invariably, or almost invariably, preceded by application of the powder and that the patient becomes sensitized to the drug by its inhalation. It is urged that powdered sulfonamide compounds should not be applied to the skin for minor conditions.

Over 200 patients, including 183 with impetigo or impetiginized seborrheic dermatitis, were treated in North Africa with 5 per cent sulfathiazole in paste of

zinc oxide or Lanette wax cream and the skin freely exposed to light. Only 1 patient (with respirator dermatitis) had the eruption described, but this was mild and soon subsided. It is considered that 5 per cent sulfathiazole in a suitable base is probably as safe as such drugs as ammoniated mercury for dermatologic therapy and gives better results. A comparison is made between this eruption and other light dermatoses, such as Hutchinson's summer prurigo and pellagra.

THE INCIDENCE AND LOCALIZATION OF ACNE. E. LIPMAN COHEN, Brit. J. Dermat. **57**:10 (Jan.-Feb.) 1945.

The author reports on the incidence of acne in a group of 500 women. The maximum incidence occurs at the ages of 19 to 21 years, but the disease is still common in the late twenties and early thirties. The age incidence in a group of men with acne was also studied and the largest group was 18 to 23 years old, but 25 per cent of the patients were over the age of 25 years. The author is of the opinion that most writers put the upper age limit of acne too low. In a study of the distribution of acne in a group of women the chin region was found to be far the most common site.

BLUEFARB, Chicago.

PREVENTION OF POST-ARSPHENAMINE JAUNDICE. J. BEATTIE and J. MARSHALL, Brit. M. J. **2**:651 (Nov. 18) 1944.

An attempt has been made to control the occurrence of damage to the liver in syphilitic patients under treatment with neoarsphenamine.

Sulfur-containing amino acids were given during that period of treatment when the expected incidence of hepatic damage was maximal.

Four preparations were tested—casein digest, casein digest reenforced with cystine, cystine and methionine.

These preparations had no effect on the over-all incidence of hepatic damage. Certain of them, however, were noticeably effective in (*a*) shifting the time of peak incidence of hepatic damage toward the end of the second course of antisyphilitic treatment or later and (*b*) moderating the severity of the damage when this did occur. The effect of the casein digest reenforced with cystine was less than that of an equivalent quantity of synthetic methionine. Cystine produced an effect similar to that of methionine only when given in large quantity on the day of the injection of the arsenical.

It was concluded that men undergoing antisyphilitic treatment should receive dietary supplements as a prophylactic measure against attacks of jaundice.

These supplements should not take the form of large quantities of cystine as this procedure may reduce the chances that the antisyphilitic treatment will be successful.

PENICILLIN PASTILLES FOR ORAL INFECTION. A. B. MACGREGOR and D. A. LONG, Brit. M. J. **2**:686 (Nov. 25) 1944.

Penicillin included in a pastille under suitable conditions is liberated in the mouth in an active form, and the concentration in the mouth can be maintained without ill effects.

Acute ulcerative gingivostomatitis (Vincent's type) simply, quickly and effectively treated in this manner. When this disease was treated in the acute stages, recurrences were seen over a three and one-half month follow-up period.

Acute hemolytic streptococcic tonsillitis seemed to respond clinically to treatment with pastilles containing penicillin.

SULPHONAMIDE ALLERGY: THE PERSISTENCE OF DESENSITIZATION. R. G. PARK, Brit. M. J. **2**:816 (Dec. 2) 1944.

The author describes two types of allergic sensitivity which can arise during sulfonamide therapy—according to whether the drug is taken internally or is applied to the skin. The internal type may take many different clinical forms, of which fever, morbilliform erythema and leukocytosis are the commonest features. In the cutaneous type the reaction is an eczematous dermatitis. In either case violent reactions are apt to follow administration of the drug by mouth.

The author feels that he has successfully desensitized his patients by giving gradually increasing amounts of the drug by mouth. For patients with the internal type it is usually possible to start with 0.1 Gm. at each dose, doubling up daily to reach 1 Gm. in four or five days. For more sensitive patients desensitization may take longer.

In persons with the eczemas a high degree of sensitivity is the rule, requiring a starting dose of 0.005 Gm. and about six weeks to desensitize. In 1 case re-investigation after one year showed that the allergy had partially returned but to only a fraction of its original level.

PENICILLIN IN CIVILIAN PRACTICE. H. B. MAY, Brit. M. J. **2**:817 (Dec. 23) 1944.

The author feels that local treatment of staphylococcic diseases of the skin with penicillin will be of great value in suitable cases.

In the treatment of sycosis a lotion was less effective than a cream which is prepared with a concentration of 200 units per gram of a base made of sterile Lanette wax and castor oil which had been autoclaved. The sterile base is prepared in large quantities, and the penicillin is added as needed.

A self-sterilizing cream is not available as yet. Tablets of penicillin proved easier to handle and more economical to use than ampules.

TWO CASES OF ERYSIPELOID TREATED BY PENICILLIN. G. A. HODGSON, Brit. M. J. **1**:483 (April 7) 1945.

Two army cooks were infected with erysipeloid after butchering a calf. Both had open wounds on their fingers, and by the eighth day of illness the clinical pictures of the two men were identical.

Each received sodium penicillin intramuscularly until totals of 485,000 units and 560,000 units had been given. Improvement was prompt, and by the fifth day both men were practically well.

SHAW, Chattanooga, Tenn.

Society Transactions

CENTRAL STATES DERMATOLOGICAL SOCIETY

Meeting Held Under the Auspices of the Cleveland Dermatological Society

JAMES R. DRIVER, M.D., *President*

GEORGE W. BINKLEY, M.D., *Secretary and Reporter*

April 29, 1944

Bowen's Disease of Penis; Late Latent Syphilis (Treated). Presented by DR. JAMES STRAUCH and DR. S. COLIMODIO.

R. M., a Negro aged 51, was previously presented before the Cleveland Dermatological Society from the department of dermatology, University Hospitals, as "A Case for Diagnosis (Chronic Balanoposthitis?)."

The penile lesions have shown no real change in the past four years. The glans penis continues to exude and is painful.

A second biopsy was made on Jan. 9, 1941. Sections showed hyperkeratosis and patchy parakeratosis. There was definite acanthosis. Rete pegs were elongated. There was variation in the appearance of cells of the malpighian layer. There were many vacuolated cells with eccentrically placed nuclei and others decidedly swollen. Some cells had circular, deeply chromatic, irregularly shaped nuclei that were surrounded by small clear spaces. The nuclei were hyperchromatic. There were many atypical mitotic figures.

Numerous lymphocytes and large round cells infiltrated the dermis. The major portion of the specimen consisted of dense connective tissue in which there were focal collections of lymphocytes and plasma cells.

Antisyphilitic therapy was begun in 1940 but was interrupted after twenty injections of a bismuth preparation and ten of oxophenarsine hydrochloride. A bismuth dermatitis appeared.

DISCUSSION

DR. ISAAC J. ARNSSON, Buffalo: To me this looks clinically as well as histologically like balanitis xerotica, although there is some vacuolation. Histologically there is absence of the dyskeratosis which would be characteristic of Bowen's disease. To my mind it is a simple balanitis xerotica.

DR. B. F. BARNEY, Columbus, Ohio: I think that this case falls into the category of cases of the disease reviewed and described clinically and pathologically by Dr. Stiles following a syphilitic infection. The appearance of the skin and the pathologic picture agree with that diagnosis. I think that it is rather an academic question of whether this is Bowen's disease or erythroplasia. They are essentially the same, but I think that it does fit into the latter classification a little better than into that of Bowen's disease.

DR. JAMES STRAUCH, Cleveland: The basis for the clinical diagnosis is Dr. Karsner's pathologic diagnosis. I am not sure whether one can differentiate histologically or not. He observed that besides the vacuolation of cells there were numerous deeply chromatic nuclei. Dyskeratosis was present; the inflammatory cells were most numerous in the connective tissue. The diagnosis was that of Bowen's disease.

DR. MYER W. RUBENSTEIN, Pittsburgh: I agree with the diagnosis of Dr. Barney. I believe that syphilis has no connection with this case.

Sarcoidosis; Tuberculoid Leprosy? Late Latent Syphilis (Treated). Presented by DR. JAMES STRAUCH and DR. S. COLIMODIO.

F. W., a Negro woman aged 43, is presented from the department of dermatology and syphilology of University Hospitals. She was previously presented before the Cleveland Dermatological Society with a diagnosis of sarcoidosis or leprosy (ARCH. DERMAT. & SYPH. **45:** 824 [April] 1942). There is no family history of any similar disease.

There are raised infiltrated circumscribed slightly nodular plaques, lighter than the surrounding skin, roughly symmetrically distributed on the face, trunk, arms and thighs. The finger joints show a fusiform puffy swelling. There is a verrucous growth on the left ala nasi. The cervical and inguinal lymph nodes are enlarged. The general physical examination revealed normal conditions. There are no areas of hypesthesia.

Tissue removed from the nose, back and arm showed a chronic granulomatous inflammation consistent with Boeck's sarcoid. Special stains revealed no acid-fast bacilli.

She has received a total dose of fifty-three injections of bismuth over a period of twenty-two months with no change in the cutaneous lesions from April 3, 1941 to June 22, 1943.

Sarcoidosis. Presented by DR. JAMES STRAUCH and DR. S. COLIMODIO.

C. W., a Negro woman aged 27, is presented from the department of dermatology of the University Hospitals. The patient was first seen, with phlyctenular conjunctivitis, in October 1940. On July 7, 1942, she complained of swelling of the parotid glands for eleven weeks. There were pain in the legs and the appearance of erythematous patches on the anterior surfaces of both lower legs after the use of sulfathiazole. At that time the only significant observation was hard, nontender enlarged parotid glands. Roentgenograms of the chest and bones revealed normal conditions. One month later, iridocyclitis of the right eye appeared; it cleared up and then recurred one month later.

One sister had typical erythema induratum at the time of the onset of the patient's uveoparotid syndrome. Two years later, she contracted pulmonary tuberculosis, with acid-fast bacilli in the sputum. C. W. was in close contact with this sister. One brother was rejected by Selective Service because of active tuberculosis.

There is slight bilateral scleral injection present, with keratic precipitates on both corneas. The parotid glands are slightly enlarged. There are erythematous nodular lesions on both legs.

The urine and the hemogram were normal. Complement fixation and flocculation reactions of the blood were negative. The plasma proteins were 6.2 Gm. per hundred cubic centimeters. The albumin-globulin ratio was 1:2. Old tuberculin elicited a positive reaction in

a 1:10 dilution, but reactions to higher dilutions were negative.

A roentgenogram of the chest made on Oct. 14, 1942 revealed enlargement of the right paratracheal lymph nodes. Repeat roentgenograms of the chest over two and one-half years showed regression of the mediastinal enlargement. An interpretation on Jan. 12, 1944 was: "There still remains bilateral diffuse mottling of the pulmonary fields, probably due to sarcoidosis."

Histologic sections of skin showed granulomatous infiltration throughout the corium with tubercle formation but without caseation.

Sarcoidosis. Presented by DR. CLYDE L. CUMMER and DR. C. G. LAROCCO.

H. W., a Negro aged 47, from St. Vincent Charity Hospital, was presented before the Cleveland Dermatological Society with a diagnosis of sarcoidosis (ARCH. DERMAT. & SYPH. **49**:446 [June] 1944).

A Case for Diagnosis (Sarcoid; Late Cutaneous Syphilid?). Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

W. D., a married man aged 33, came to the Cleveland Clinic Foundation Hospital on March 13, 1944 with a lesion involving the right upper eyelid. His past history was unimportant. However, he states that his father and mother have syphilis and that a sister seven years younger than he has been treated for interstitial keratitis. Before he came to the clinic, five serologic tests for syphilis were made, all of which elicited negative reactions.

Nine months ago, he sustained a painful injury to the right eye, caused by a thrown apple. The trauma did not cause an ecchymosis. The cutaneous lesion for which he is presented developed six weeks later. The right upper eyelid became swollen and red. The lesion developed rapidly but it has not changed in size during the past five or six months. There has been no discomfort; however, the enlarged upper eyelid has partially obstructed the vision of the right eye.

There is a dull red, smooth, disklike plaque of doughy consistency, involving most of the right upper eyelid. On palpation, the plaque consists of a well demarcated infiltration, which extends into the fold of the eyelid. The thickest portion of the lesion involves the margin of the lid. The eyelashes are absent. The lesion has the appearance of a chronic granuloma. There is no telangiectasia and no pearly deposit which is seen in a basal cell epithelioma.

Histologic examination showed the following conditions: The epidermis was normal, except for thinning and obliteration of interpapillary pegs by the infiltrate in the corium. The tissue of the papillary and subpapillary portions was dense and showed a slight amount of lymphocytic infiltration. In the deeper portion of the corium there were poorly demarcated areas of cellular infiltration. The infiltrate was composed of lymphocytes, large mononuclear cells and many plasma cells. Some of the arterial vessels were thickened and partly hyalinized; others showed proliferation of the intima. In a separate section of the subcutaneous tissue, the infiltration located between striated muscle fibers consisted mostly of lymphoid cells. In other areas there were well demarcated nodules composed of large mononuclear and epithelioid cells, partly or completely surrounded by lymphocytes and an occasional plasma cell.

Physical examination shows enlargement of the epitrochlear lymph nodes. There are no other signficant changes. The roentgenogram of the chest showed normal conditions. An intradermal test with 1:100 dilution of old tuberculin elicited a negative reaction. The urine and the hemogram were normal. The Wassermann and Kahn reactions of the blood were negative.

Since March 13, 1944, four roentgen ray treatments of 100 r each with a 1 mm. aluminum filter have been given to the lesion on the eyelid. The lesion has decreased in size.

DISCUSSION OF FOUR PRECEDING CASES

DR. HUGO HECHT, Cleveland: In the case of C. W. the roentgenograms show enlarged paratracheal lymph nodes and the biopsy shows cells with tuberculous inflammation. I regard this as a tuberculid. In the case of H. W. the lesion looks like lupus rather than a sarcoid. The lesion is soft and not indurated, and through the exclusion of other diagnoses, I should call it lupus tumidus. In the case of W. D., I favor the diagnosis of syphilis rather than that of sarcoid.

DR. C. G. LAROCCO, Cleveland: With reference to the case of H. W., I refer to the sarcoids seen at St. Vincent Charity Hospital. If the disease were lupus, there should be a sign of ulceration over this long period. The lesion has persisted as a noninflammatory tumor. Roentgenograms of the long bones show conditions consistent with the diagnosis of sarcoid.

DR. HOWARD J. PARKHURST, Toledo, Ohio: In the case of C. W., the question arises as to whether the eruption is sarcoid or papulonecrotic tuberculid. In the cases of papulonecrotic tuberculid that I have observed the lesions have had a much more rapid course than these, and there has been scarring after the involvement has been present this length of time. I feel that lesions with the slow course shown by this one are more likely to be lesions of sarcoid. In the case of W. D., I am strongly in favor of sarcoid.

DR. STANLEY CRAWFORD, Pittsburgh: In the case of C. W., several things might be thought of, among them lichen obtusus corneus. I did not see much evidence of sarcoid. The patient has an anergy, which is against papulonecrotic tuberculid but is encountered in patients with sarcoid or lichen obtusus corneus. The other cases I think are definitely instances of sarcoid.

DR. FRANZ L. BLUMENTHAL, Detroit: I should think that clinically one could not distinguish in the case of H. W. whether the eruption is sarcoid or lupus. I have seen cases of lupus in which there was no tendency toward ulceration. I suggest animal inoculation.

DR. JOHN E. DALTON, Indianapolis: The department of internal medicine of the University of Indiana School of Medicine has been following several cases of erythema nodosum with sarcoid infiltration in the lungs. It would be interesting to follow these cases.

DR. MYER W. RUBENSTEIN, Pittsburgh: Do the erythema nodosum nodules disappear when the pulmonary lesions clear?

DR. JOHN E. DALTON, Indianapolis: They have improved, but they have not completely disappeared. In one of the cases I had, there was a lesion above the clavicle. At the time operation was performed, the lesion was removed. It showed a typical sarcoid structure.

DR. HAROLD N. COLE, Cleveland: I am disappointed that there has been no remark regarding the case of F. W. This patient has been under observation for about three years. The process has regressed somewhat. From the illustrations of this patient in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**45**:824-827 [April] 1942) one may see that the lesions were

more noticeable then than they are at present. The patient was seen by two leprologists, and both made the diagnosis of tuberculoid leprosy. I was eager to see whether any one would make a diagnosis of leprosy. She has all the characteristics of sarcoidosis. Rabello (Rabello, F. E.: A lepra incaracteristica no experiencia do Sanatorio Padre Bento, *Rev. brasil. de leprol.* **11**: 115-132 [June] 1943) from Brazil, has reported on a series of patients with tuberculoid leprosy showing all the findings of sarcoidosis, including the anergy to tuberculin and the osseous changes. Sometimes it is almost impossible to distinguish between these two diseases.

DR. LOREN W. SHAFFER, Detroit: How are they differentiated?

DR. HAROLD N. COLE, Cleveland: Of course in the tuberculoid type of leprosy it is almost impossible to find the organisms. The disease is well under control of the patient's immune powers. The patients are supposed not to be dangerous to any one else, and the disease does not cause any trouble. In this particular case the process is gradually regressing.

DR. STANLEY CRAWFORD, Pittsburgh: It is the impression in Scandinavia that sarcoid is a form of leprosy, but the world has not accepted that, especially in the southern part of the United States, where the disease is more prevalent.

DR. ISAAC J. ARNSSON, Buffalo: If one could go by therapeutic tests, one could consider the difference in response of sarcoid and leprosy. Some of the patients do improve considerably after using chaulmoogra oil. In patients with Boeck's sarcoid regression took place after fourteen injections of chaulmoogra oil. This case certainly looks like one of leprosy. I tried to palpate the nerve around the neck. There was no disturbance of esthesia. I think that the eruption is a sarcoid.

DR. C. K. HAISLEY, Detroit: I think that the radiologists can offer help in the process of sarcoid. There is one living in Detroit now who is particularly interested in this type of sarcoid. If you care to send him any films you may have, he will be pleased to offer any help he can. I also studied the films of the hands, showing areas of erosion from pressure. In Detroit many cases have been found lately, and the radiologists have proved to be right.

DR. HARRY L. CLAASSEN, Cincinnati: In regard to the case of F. W., Dr. Cole stated that the patient is improved. In cases in which a sarcoid is improving, usually the sarcoid improves but the patient's physical condition usually becomes worse. Is that true in this case?

DR. GEORGE W. BINKLEY, Cleveland: I think that the patient's physical condition has not changed in the past year.

DR. JAMES STRAUCH, Cleveland: In regard to the case of F. W., I should like to call attention to the fact that the patient had a positive Wassermann reaction. On that basis antisyphilitic therapy was started. Nothing has appeared in the history of her family. The positive Wassermann reaction may be due to leprosy. In the case of C. W., the family history shows that the patient has a sister who had erythema induratum as well as pulmonary tuberculosis. She also has a brother who has active tuberculosis. She was in close contact with open tuberculosis.

DR. E. W. NETHERTON, Cleveland: Clinically, the lesion in the case of W. D., presented by the Cleveland Clinic Foundation Hospital, looks like a granuloma. It could easily be a gummatous process or a sarcoid. As Dr. Parkhurst has pointed out, the anergy to tuberculin and the repeatedly negative serologic reactions of the blood are against the diagnosis of late cutaneous syphilis. This does not rule out syphilis as a diagnosis, however. Histologically, the lesions consist of areas of cellular infiltration, consisting chiefly of lymphocytes and large mononuclear cells. There are, however, numerous plasma cells. The histologic structure favors the diagnosis of syphilis more than of sarcoidosis.

Postsyphilitic Dyschromia; Late Dyschromic Pinta? (Treated). Presented by DR. JAMES STRAUCH and DR. G. W. BINKLEY.

M. K., a white woman aged 64, is presented from the department of dermatology of the University Hospitals. She was presented previously before the Cleveland Dermatological Society as "A Case of Erythroderma of the Hands and Wrists in a Syphilitic Patient" (ARCH. DERMAT. & SYPH. **39**:1073 [June] 1939). No history of alopecia, genital sore or inguinal adenopathy was obtained. She has always lived in Cleveland. She has been married to her second husband for twenty-three years. There is one daughter, aged 21, who is living and well and with no syphilis, and three children by the first husband. They are living and well.

One year after antisyphilitic treatment was begun, there remained a glovelike area of uniform pigmentation with slight erythema. At present, six years after the start of therapy, the erythroderma has disappeared, leaving slight hyperpigmentation on the dorsum of the hands and various areas of depigmentation on the flexor surfaces of the forearms. There are sharply defined triangular areas of depigmentation on the flexor surfaces of the wrists. The base of each triangle is at the level of the wrist joint. Cigaret-paper-like superficial atrophy is found proximal to these triangles.

The patient was treated with alternating courses of bismuth and oxophenarsine hydrochloride. At the end of sixteen months' treatment, the Wassermann reaction was still positive. At thirty months the Wassermann, Kline diagnostic and Kline exclusion reactions of the blood were still strongly positive. Three years later repeat serologic tests showed the Wassermann reaction to be negative and the Kline diagnostic and Kline exclusion reactions positive.

DISCUSSION

DR. ROBERT C. JAMIESON, Detroit: After seeing the photographs of the original eruption, while I should not like to dispute the word of any one who has been taking care of the patient, I must admit that I have never seen an eruption of this type due to syphilis. Treatment might readily clear up an eruption of that kind. As far as the pigmentation is concerned, one finds a dyschromia from any kind of chronic inflammation.

DR. ISAAC J. ARNSSON, Buffalo: Histologically, I think the picture is typical of syphilis.

DR. DANIEL J. KINDEL, Cincinnati: It has been our good fortune in Cincinnati to hear Dr. Martinez, who gave a comprehensive story of pinta. In early pinta there are superficial lesions in the eruptive stage which disappear rapidly. Histologically the lesions in this case do not fit in with the active lesions of pinta as he described them. Diagnoses which I feel could be considered with more weight than pinta would be pellagra and, secondly, possibly an inflammatory process due to rubber gloves which causes depigmentation. On what was the diagnosis of pinta based?

DR. GEORGE W. BINKLEY, Cleveland: I suggested the diagnosis of late dyschromic pinta of the skin for this patient in 1939, one year after antisyphilitic therapy was begun. At this time it was too late to establish the causative spirochete in the twenty year old cutaneous lesion. This demonstration would have been preponderant evidence in favor of pinta. Since the patient lives in the United States, my colleagues have regarded the spirochete in this case as Treponema pallidum, but I believe that if this woman were a resident of Cuba, Mexico or South America, where many lesions of late pinta are seen, late cutaneous pinta would have been the diagnosis, for the following reasons: In 1938, the involvement of the flexor surfaces of the forearms was of twenty years' duration. On the flexor surfaces of the wrists were triangular areas of depigmentation, typical of pinta. The lesions were mildly pruritic. Complement fixation reactions and Kline reactions of the blood were strongly positive, and the histologic changes were consistent with those of late pinta. One year later the erythroderma was almost gone. There was a slow but continuous improvement from administration of oxophenarsine hydrochloride and bismuth. At this time, six years after treatment was begun, there is only hyperpigmentation of the borders of the former erythroderma of the forearm. A triangular area of permanent depigmentation remains on the flexor surfaces of the wrists. I have seen a pintoid picture on the flexor surfaces of the forearms in North American Negroes with early syphilis, and I believe that Treponema pallidum can simulate pinta in some of its aspects. Dr. E. P. Liberthal has reported 3 cases of late or tertiary dyschromic pinta (*J. A. M. A.* **123**:619 [Nov. 6] 1943).

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Treatment consisted of continuous use of moist antiseptic dressings of surgical solution of chlorinated soda and weak silver nitrate solution with benefit. Zinc peroxide medicinal dressings were of no value. After a combined course of emetine hydrochloride and chiniofon, the diarrhea subsided and the ulcers healed. Sulfathiazole, previously tried, had been of no value.

In September 1943 she was again hospitalized for three weeks, because of recurrent diarrhea and the appearance of more ulcers on her legs. Healing of the ulcers occurred when the diarrhea was controlled by the administration of succinylsulfathiazole. When use of this drug was discontinued, another exacerbation developed with more ulcers, and she was hospitalized for the third time, from Dec. 18, 1943 to Jan. 10, 1944. The drug was again administered, and healing of the ulcers occurred, together with relief from the colitis. Since then she has continued to take the drug, without any further evidence of colitis or ulceration of the skin.

The urine was normal. The hemogram revealed a moderate degree of secondary anemia.

DISCUSSION

DR. HARTHER L. KEIM, Detroit: I agree with the diagnosis as suggested and feel that the lesion on the left calf still shows activity. The honeycomb appearance of these lesions shows that. I think that as soon as penicillin is available it should be used.

DR. ISAAC J. ARNSSON, Buffalo: Similar good results have been obtained from the use of tyrothricin.

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DR. JAMES R. DRIVER, Cleveland: This patient was presented last year with a diagnosis of amebiasis cutis, partly because the ulcers resemble the ulcers of that disease and partly because of the fact that this patient's trouble started after she visited the Chicago World's Fair. She has been in the hospital on three different occasions, and numerous attempts have been made to demonstrate amebas in the stools, but none have been found. Her attacks are timed exactly with her attacks of colitis. At that meeting Dr. Netherton suggested that this case might fit into the group Dr. Brunsting presented in 1930. I looked up this article and found that 5 cases were reported on at that time. The photographs accompanying the article have convinced me that this case falls into that group. In their cases they found that benefit was obtained by treating the patients for amebic dysentery. At that time, of course, the sulfonamide preparations were not available, so I treated this patient on her first admission with emetine and she did improve somewhat. The last two times that she was admitted I used succinylsulfathiazole. Of course the dose is almost unlimited and can be kept up for any length of time. This patient responded almost miraculously to this treatment. She has had no trouble now for several months. The diarrhea is kept under control by the drug, and the lesions are practically well. She has had no exacerbations at all. She takes a week or ten days' vacation from the drug, then starts it again, about 4 Gm. a day. The organism isolated in our case was a hemolytic staphylococcus.

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The blood calcium level was 10 mg. and the blood phosphorus level 3.9 Gm. per hundred cubic centimeters.

A section of a nodule removed for histologic examination showed a thin epidermis covered by a thin layer of hyperkeratosis. Most of the interpapillary pegs had been obliterated by changes in the corium. Throughout the corium there was a diffuse, and in places fairly dense, polymorphous cellular infiltrate. The multiplicity

of cell types was striking. The infiltrate was composed of lymphocytes, large mononuclear cells, leukocytes, eosinophils, plasma cells, endothelial cells and connective tissue cells. There were pyknotic cells and some cellular debris in the delicate connective tissue stroma of the densely infiltrated areas.

The cutaneous nodules have decreased in size after seven low voltage roentgen ray treatments during the four months.

DISCUSSION

DR. HARTHER L. KEIM, Detroit: I do not think that this is acrodermatitis chronica atrophicans; the process has too many hypertrophic characteristics. The nodule definitely makes one think of mycosis fungoides.

DR. MYER W. RUBENSTEIN, Pittsburgh: I believe that this case is typical and characteristic.

DR. E. W. NETHERTON, Cleveland: One year ago we presented this case with a question regarding the possibility of mycosis fungoides. This was based on the histologic changes observed in a nodule which had been removed. I think that Dr. Keim's remarks are pertinent because of the changes observed in the tissue which was removed, and which showed multiplicity in type of cells in the infiltration. The changes are strongly in favor of the diagnosis of mycosis fungoides. At the previous presentation Dr. R. E. Barney discussed the case, and he felt that this possibility should be kept in mind. At that time he discussed the case he had observed, which was a case of acrodermatitis atrophicans vasculare terminating in lymphoblastoma. As for the sclerodermatous changes, these are seen in acrodermatitis atrophicans. This patient has the ulnar bands and the scleroderma-like changes on the legs which are sometimes seen in this disease.

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The face is still involved by a grouped discrete brownish papulosquamous eruption especially prominent at the inner portion of the left eyebrow and over the forehead. There is a diffuse slightly raised moist grayish white proliferative involvement of the soft palate, tonsillar fossae, posterior pillars and a portion of the pharynx. There are also two small superficial nontender granular ulcers at the palatine junction. The patient's general health has remained good.

Treatment has consisted of cryotherapy, gold, acetarsone, bismarsen, chaulmoogra oil, radium bulb and electric cautery. Some improvement resulted from cryotherapy. Gold therapy was effective in causing remissions from time to time of the lesions on the face.

DISCUSSION

DR. STANLEY CRAWFORD, Pittsburgh: I disagree with the diagnosis as presented. There is no appearance of lupus vulgaris to the eruption. The lesions of the eyebrows appear to be impetiginized.

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Aside from the usual infections of the upper respiratory tract, the patient's health has been excellent. She states that she sunburns readily and that excessive exposure to the sun results in an exacerbation of the eruption. There is no family history of tuberculosis.

On the bulbous portion of the nose and over the lips are flat raised firm confluent lesions, varying from 3 to 10 mm. in diameter. The surface of these lesions is rough and hypertrophic, with some areas of exudation and crusting. Similar lesions are present on the prominence of the right cheek and below the right eye. There are some small red and brown papular and follicular lesions scattered over the dorsa of the hands and wrists.

Histologic examination of a piece of skin removed from one of the lesions on the side of the nose revealed a well developed horny and granular layer of the epidermis. There were a few cells in the mucosal and basal layers with vacuolation of the cytoplasm and distortion of the nuclei. In the upper portion of the corium a moderate degree of edema was present, and numerous dilated blood vessels were seen. Some perivascular small round cell infiltration and several focal accumulations of small round cells and epithelioid cells were found in the same area. There were numerous large sebaceous glands throughout the entire section, and several keratotic follicular plugs were present.

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Dystrophia Mediana Canaliformis. Presented by Dr. Max E. Krause for Dr. Harold N. Cole and Dr. James R. Driver.

D. K., a white woman aged 41, complains of a deformity of the left great toe nail. The nail was normal until three years ago, when there began to develop a median longitudinal deformity with a bluish discoloration as if traversed by a blood vessel. Recently, the bluish discoloration disappeared and desquamation ocurred. There are no subjective symptoms or history of previous injury to the nail.

The abnormality of the left great toe nail consists of a 3 mm. wide centrally located longitudinal furrow or groove extending from the base to the free edge. The groove is filled with soft cornified nail debris. The nail fold, bed and matrix appear normal. All other nails are normal.

Dystrophia Mediana Canaliformis. Presented by Dr. Max E. Krause for Dr. Harold N. Cole and Dr. James R. Driver.

J. B., a white man aged 54, was told that at 1 year of age he had an infection of the third finger of the left hand with a subsequent loss of its nail. With regrowth of the nail a median longitudinal deformity appeared which has persisted unchanged. The deformity is asymptomatic.

The patient exhibits a central longitudinal deformity of the nail of the third left finger. It consists of a ridge that seems to originate in the nail fold and extend outward, forming a shallow furrow or groove within the nail plate. The other nails are normal in appearance. There are no cutaneous defects or other abnormalities.

DISCUSSION OF TWO PRECEDING CASES

Dr. C. K. Haisley, Detroit: I have seen a good many such lesions on finger nails. In fact, I have one on one of my own finger nails. It resulted from handling too much radium without using enough caution. I have also seen them on radiologists who remove foreign bodies.

Dr. Ralph R. DuCasse, Cincinnati: I also wonder whether in the use of radium the contact with the radium was actually made or whether it was from a long distance exposure.

Dr. C. K. Haisley, Detroit: That is hard to tell. Frequently one has to use the fingers when in a hurry.

Dr. James R. Driver, Cleveland: The question is whether this condition is a nevus or whether it is due to trauma. The case of D. K. seems to be an instance of the second type; however, the patient (41 years old) has had the condition for only a year and gives no history of trauma. Similar changes can be seen in persons who have had too much radiation, particularly in physicians and technicians who use roentgen rays and radium, and yet the affected areas do not look exactly like this one. The growth will separate after it has extended about the median line of the nail, and then the process starts again as the nail grows out. In the case of the man who has had it since infancy, he was told that he had had some sort of infection and he has had this process ever since. In the case of D. K., trauma is probably the causative factor. Clinically, the two lesions look different.

Dr. B. F. Barney, Columbus, Ohio: In the case of the man, I think that one is dealing with trauma, a growth from the nail bed. Owing to insufficient blood supply, the nail separates as it grows out. Regarding the case of the woman there is a lesion which seems to be an actual tube of cells which erupts; then the process starts all over again. I agree with the diagnosis for the woman and disagree with the diagnosis for the man.

Congenital Ectodermal Defect. Presented by Dr. Don R. Printz and Dr. Sam Ayres III.

H. K., a white man aged 27, presented from the department of dermatology and syphilology, Cleveland City Hospital, service of Dr. Harold N. Cole and Dr. James R. Driver, has the complaint of being unable to tolerate heat. He cannot remember ever sweating and has always had a sparsity of hair on his body. There is no family history of similar disturbances or epilepsy. He is married and has one normal son.

The skin on the entire body is soft and of fine texture with absence of moisture on palms and soles. On the face, especially around the eyes, mouth and sides of the neck, are many yellowish brown papules about 1 to 2 mm. in diameter which tend to be arranged in a linear fashion. The eyes are normal. The nose is small, with a depressed bridge covered with atrophic skin and lined with an atrophic mucous membrane. The lips are thick and dry. The only erupted teeth are two lateral incisors and two canine teeth in the upper jaw and two in the lower jaw. The hair on the scalp and chest and in the axillas is lanugo-like; that on the face is normal, except for an area of alopecia over the right mandible. There is no pubic hair. The nails are normal.

The hemogram and urine were normal. The blood chemistry was normal. The Wassermann reaction of the blood was negative on nine occasions, while the reaction to a Kline diagnostic test varied from negative to strongly positive. The spinal fluid was normal. Roentgenographic examination of the chest showed normal conditions and of the tibia showed no evidence of periostitis.

Histologic examination of a section of skin taken from an axilla showed mild hyperkeratosis, keratotic plugs in dilated follicular orifices and intracellular edema of the epidermis. The hair follicles and sebaceous gland were normal. A specimen taken from the skin of the neck showed moderate hyperkeratosis, a small area of parakeratosis and mild intracellular edema of the epidermis. There were a few small hair follicles present. The follicular orifices were dilated and filled with keratotic plugs. Some sebaceous glands were normal, while others were disorganized. No sweat glands were found. The epidermal layer was invaginated at places to form relatively large cystic spaces filled with keratotic material.

DISCUSSION

Dr. Roy L. Kile, Cincinnati: In this case I am in favor of a diagnosis of poikiloderma atrophicans vasculare. Inasmuch as the nails are normal, the hair is normal and there is definite atrophy and teliangectasia, I believe that this is the most likely diagnosis.

Dr. Howard J. Parkhurst, Toledo, Ohio: I felt that this case is a good instance of congenital ectodermal dysplasia as described by Goeckerman.

Dr. Harold N. Cole, Cleveland: In my opinion, as we more carefully analyze the ectodermal dysplasias, we are going to find more and more varied manifestations of this unusual condition. In one case it may be a more extensive involvement of the skin, in another the teeth, in another perhaps the eyes, etc. Moreover, it may well be that we shall gradually recognize all variations from a complete ectodermal dysplasia such as first described by Clauston (Clauston, H. R.: The

Major Forms of Hereditary Ectodermal Dysplasia [with an Autopsy on the Anhidrotic Type], *Canad. M. A. J.* **40**:1-7, 1939) down to the individual with but a few unusual involvements that will test our powers of observation and analysis to place them properly. And, too, we may find occasionally types involving not only ectodermal structures, but also mesodermal tissue, that is, bone.

Trichophytosis Barbae. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

R. K., a white farmer aged 37, was first seen in the Cleveland Clinic Foundation Hospital on April 28, 1944. He noticed three small round red papules on the left side of his neck, two months ago. These increased in size rapidly, each one reaching the size of a silver dollar in about five days. The surface of each of these superficial lesions appeared as a series of raised red concentric rings. These disappeared in about two weeks with applications of an "eczema salve," leaving three or four small papules and dark red macules, where the lesions had been. At this time, two new lesions appeared on the upper lip. These grew slowly into crusted exuding nodules which persisted about a month and then disappeared, leaving erythematous areas. During this time, the patient received biweekly injections of a calcium preparation and soothing local applications. Four weeks ago, several new lesions appeared on the lower lip and chin. These have developed slowly to their present extent.

The patient disposed of a bull four months ago. This bull had a swollen jaw, which was discharging pus from several openings.

There are three closely adjacent crusted raised indurated nodular lesions, each about the size of a silver dime, on the left side of the lower lip. These are surrounded by erythematous areolas and are exuding a purulent discharge. Similar lesions are present on the right side of the chin and in the submental region. A few small pustules are seen in all the lesions. Several smooth or scaly firm red nodules and papules are scattered over the bearded area of the face and neck. Most of the hairs in all involved areas are easily removed. There are two purplish erythemtous macules involving most of the upper lip.

Microscopic examination of a potassium hydroxide preparation of hairs from the involved areas showed innumerable small spores and hyphae, located in and surrounding the hair shafts.

The Wassermann and Kahn reactions of the blood were negative. The blood sugar level and the hemogram were normal.

DISCUSSION

DR. STANLEY CRAWFORD, Pittsburgh: This disease could be considered actinomycosis. Has search been made for yellow bodies? One could still consider an uncomplicated sycosis.

DR. ROY L. KILE, Cincinnati: At times tinea barbae is rather difficult to cure. This is contrary to the ease with which fungous infections of the scalp are usually cured by local therapy in the Middle West. Many years ago Dr. M. F. Engman Sr. reported on the intravenous injection of typhoid vaccine in cases in which the disease is resistant to local therapy. The results were apparently favorable.

DR. HOWARD J. PARKHURST, Toledo, Ohio: I have seen an occasional instance of this type. All the patients have been farmers; in all the disease has been due to the bovine type of organisms, and all have responded well to applications of diluted iodine.

DR. E. W. NETHERTON, Cleveland: This case presents one feature which is thought to be common in sycosis barbae; namely, that the upper lips are seldom involved. This patient did have a superficial erythematous scaly lesion on the upper lip at the onset of the eruption, but this has cleared up. Against the diagnosis of actinomycosis is the fact that the lesions are not as deep as those of actinomycosis, the surfaces of the lesions in this case are crusted, and there are numerous follicular pustules on the lesions. The demonstration of the presence of the spores and hyphae in and about the hair and the absence of granules in the exudate were considered sufficient to rule out the possibility of actinomycosis.

Angioendothelioma of the Skin. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

J. F., a married man aged 52, came to the Cleveland Clinic Foundation Hospital on July 12, 1940, because of an eruption on the feet of six months' duration. His past and family histories were noncontributory. The eruption started with desquamation between and beneath the toes. Four months later the dorsal surface of the feet became red and edematous, and a purulent exudate developed between the toes.

When he first came to the clinic, there was a moderate amount of dry scaling between and beneath the toes. There were no fissures in the interdigital spaces. However, between the second and third toes of the left foot, there was a small ulcer. The patient stated that recently he had removed a small "corn" from this interdigital space. There were slight edema of the lower portion of the legs and a poorly demarcated subacute erythematous edematous scaly dermatitis on the dorsal surface of each foot. Hyphae were not found in potassium hydroxide preparations of material removed from interdigital spaces.

After rest in bed, magnesium sulfate soaks and application of a mild tar ointment, the eruption disappeared. He remained free of the eruption until early in 1943. In December 1943 he was admitted to the hospital, because of partial cardiac decompensation. At this time there was a polymorphous eruption involving the feet, the lower portions of the legs and the knees and hands. There were fairly well demarcated, light red gyrate scaly plaques on the soles, the dorsal and lateral surfaces of the feet and the inner surfaces of the ankles and lower portion of each leg. The scales were large, gray, dry and adherent. The epidermis was thin and slightly atrophic. There was no induration.

There was a poorly circumscribed soft brownish pink smooth plaque the size of a half-dollar just above the right knee.

There was a similar but smaller lesion near the left knee. The lesion on the left knee was removed for histologic examination.

The third type of lesion was located on the dorsal and lateral surface of the right fifth finger, the adjacent area of the dorsal surface of the hand and the lateral surface of the right ring finger. This lesion was a brownish red smooth well demarcated indurated plaque. After the removal of a biopsy specimen from this plaque, the lesion showed decided involution. A similar but smaller indurated nodule was present on the lateral surface of the left ring finger. Four treatments of 75 r of unfiltered roentgen rays have been given to these lesions on the hands and feet. The induration of the lesions on the hand has almost disappeared, and the plaques on the feet and legs are not as erythematous as before. However, the chief characteristics of the eruption have not changed.

Tissue was removed from the plaques on the right hand and the left knee and an erythematous scaly plaque on the inner surface of the left leg for histologic study. The section from the edematous plaque showed an inflammatory reaction of the corium and subcutaneous tissue. The epidermis was covered with a layer of hyperkeratosis but was otherwise normal. Throughout the corium there were areas of perivascular infiltration, composed of lymphocytes, large mononuclear cells and an occasional neutrophilic leukocyte. Many of the vessels were dilated. The cellular infiltrate in the subcutaneous fat included lymphocytes, fibroblasts and phagocytes containing a golden brown pigment.

A section from the hand showed a thick layer of hyperkeratosis, but otherwise the epidermis was normal. There was a diffuse cellular infiltration of lymphocytes and large mononuclear cells throughout the corium with a richly cellular proliferation of the connective tissue, and in the upper portion of the corium there were many irregular clear epithelium-lined spaces. There were also clear spaces without definite cellular lining, which could be interpreted as artefacts.

Tissue from the lesion near the left ankle showed atrophic epidermis covered with a thick layer of hyperkeratosis. The granular layer was patchy and indistinct. The rete mucosum was thin, and the cells stained poorly. The basal layer was intact. The interpapillary pegs were obliterated. In the papillary layer and upper portion of the corium there was a vascular network of sinusoidal character surrounded by polygonal, oval and fusiform endothelial cells, some in mitosis.

Dr. Harry Goldblatt made a histologic diagnosis of subacute inflammation of dermis and subcutaneous tissue in the lesion removed from the hand and knee, but he considered the lesions of the leg as angioendothelioma of the skin, probably arising from vascular hamartoma.

An intradermal tuberculin test (purified protein derivative) elicited a positive reaction. The Wassermann and Kahn reactions of the blood were negative. The hemogram and urine were normal.

DISCUSSION

DR. ISAAC J. ARNSSON, Buffalo: I think that multiple idiopathic hemorrhagic sarcoma should be considered. Histologically, there are elements which speak for it. There are a number of blood vessels and sarcoma-like invasion of the cutis.

DR. E. W. NETHERTON, Cleveland: We seriously considered the diagnosis of sarcoma of Kaposi in this case, but because of the lack of hemorrhages and pigmentation this diagnosis was ruled out. Dr. Goldblatt's opinion is that although there are some features which favor the diagnosis of Kaposi's sarcoma, in the final analysis the histologic observations rule out this possibility. The diagnosis with which this patient was presented is a pathologic one. The angioendotheliomatous change is striking in the sections of the tissue taken from the lower portion of the leg.

Scleroderma en Coup de Sabre. Presented by DR. DONALD N. MACVICAR for DR. HAROLD N. COLE and DR. JAMES R. DRIVER.

M. F., a white boy aged 13, complains of a lesion of the scalp of three years' duration. The lesion started as a small spot on the right side of the forehead and has gradually extended back over the scalp. Some pruritus in the area has been noted at times. He can remember no trauma in the region of involvement.

On the right side of the scalp, extending from the hair line above the region of the right eye backward over the head, is a bald linear lesion, 6 by 1.2 cm. in size. The skin of the area is of an ivory color and is bound firmly to the underlying skull. The border of the lesion has a delicate pink color. The entire area is depressed below the surface of the scalp into an underlying furrow in the skull.

Thyroid extract was prescribed and a soothing ointment applied locally. Since the inception of therapy the lesion has increased slightly in size.

DISCUSSION

DR. HARTHER L. KEIM, Detroit: I have seen this disease before, and I remember that in both cases it progressed down over the face. I thought that the alopecia resembled pseudopelade. There are slight itching and slight scaling suggestive of alopecia. The disease appears to be located in the central part of the scalp and has made a definite furrow into the skull.

DR. HAROLD N. COLE, Cleveland: It would be unusual to see pseudopelade limited to one area on the skull. Usually the lesions are found freely distributed. Moreover, this lesion is more or less linear in type. These cases of saber cut scleroderma may involve the scalp alone, the forehead alone, or both combined. The picture presented here with the involvement of the bone would support the diagnosis of scleroderma en coup de sabre.

Mycosis Fungoides. Presented by DR. B. LEVINE.

C. N., is a white woman aged 37. Her mother died fifteen years ago during menopause. Her father, three sisters and two brothers are living and well. No brothers or sisters died. There is no history of tuberculosis or malignant neoplasms in the family.

She had an appendectomy eighteen years ago and a thyroidectomy fifteen years ago for a toxic goiter. There is no history of eczema, psoriasis or other eruption prior to the present illness. She was delivered of a normal child two years ago. The patient believes that she is pregnant at present.

The present illness began three years ago with an eruption on the body. This did not itch at first, but itching started when she became pregnant. The eruption did not get worse during the course of the pregnancy, but after the birth of the child the lesions became more numerous, pruritic, scaly and thickened, with some tumor formation. The eruption then spread over the face, neck and limbs as well as the body and thighs. These were large confluent plaques, dark red, thickened, infiltrated and scaly and circinate and gyrate in shape, leaving areas of normal skin between. Some of these plaques were somewhat elevated. Many of them, especially on the face and upper part of the body, are regressing from roentgen ray therapy the patient received at the Mayo Clinic. A tumor mass 2.5 cm. high on the neck has cleared up with roentgen ray therapy.

The Kline slide precipitation reaction was negative throughout. The urine was normal. The hemogram is as follows: red blood cell count, 3,810,000; white blood cell count, 6,850; hemoglobin content, 75 per cent; polymorphonuclear neutrophils, 69 per cent; lymphocytes, 14 per cent; monocytes, 12 per cent, and eosinophils, 5 per cent. The red blood cells and platelets appear normal.

A section of the skin revealed that the epidermis was thicker than average. Interpapillary projections were larger than average, coarse and blunt. In the upper portion of the dermis just beneath the surface epithelium and in the papillary projection there was considerable round cell infiltration composed of lymphocytes, monocytes and plasma cells. There was an increase in the

number of fibroblasts and capillaries in this section. No giant cells were seen. The cellular infiltrations were most evident in perivascular locations but diffusely involved the entire upper part of the dermis. No areas of necrosis were present. The deeper layers of the epidermis showed no appreciable cellular infiltration except in the stroma immediately about sebaceous glands and hair follicles, where there was slight fibroblastic proliferation and infiltration by wandering cells similar to those which richly infiltrate the upper portions of the dermis.

DISCUSSION

DR. STANLEY CRAWFORD, Pittsburgh: I am of the opinion that roentgen ray therapy is the only efficient treatment. The ultimate outlook is hopeless. To keep the lesions under control, one may as well treat them with roentgen rays. The question in each case is how many units of roentgen ray should be given.

DR. FREDERICK M. JACOB, Pittsburgh: For a matter of five years my colleagues and I have been using roentgen rays and chaulmoogra oil when tumors occur. We have never decided whether chaulmoogra oil does any good, but I am giving it a fair trial.

DR. B. LEVINE, Cleveland: The diagnosis, both clinically and microscopically, is obvious. I have treated the upper part of the body with filtered roentgen rays. The rest was left untreated so that some unaltered lesions would remain for this meeting.

Systematized Epithelial Nevus. Presented by DR. JOHN A. GAMMEL.

Mrs. R. C., a white woman aged 28, has two healthy children, 4 and 5 years old. When the patient was 6 weeks old, a "baby rash" was noticed, which persisted and gradually spread. It has now been stationary for many years. Three years ago, after the tops of some of the lesions had been scraped off, a vesicular outbreak occurred which lasted for several weeks and caused great discomfort. There are no subjective symptoms. The patient enjoys good health.

The eruption is almost generalized and is roughly symmetric. The face is clear, except for some rough spots at the side of the nose. The skin in general is dry, and the upper part of the back shows a large area studded with punctate keratoses.

The outstanding lesions are in the folds of the extremities: the anterior and posterior axillary folds, the cubital fossae and in the popliteal spaces. The disease is most evident in the right groin. In these areas there are linear lesions made up of more or less elevated, and in places verrucous, efflorescences. The softer lesions are of skin color, and the larger and more elevated ones light to dark brown.

Confluent lesions extend in streaks from the lateral aspect of the right wrist to the palm, where they fan out and become hard and wartlike. Here the color shows a yellow hue. The eruption is to a lesser degree present on the left hand. A heavy streak extends from the right ankle to the big toe. There are lesions on both insteps.

The stratum corneum was thick and contained a few widely spaced pillars of parakeratosis. The lower surface of the horny layer projected into sella turcica–shaped valleys, formed by a wavy epidermis.

The main disturbance in the tissue was in the basal layer. The basal cells had a low cuboidal shape, and there was intracellular edema in many. Above these low cells the rete cells showed an amorphous degeneration. These areas were more eosinophilic than the normal rete Malpighii. In places the full thickness of the rete showed eosinophilic degeneration of the squamous cells. More severely involved areas of the epidermis were fragmented.

DISCUSSION

DR. E. W. NETHERTON, Cleveland: I should like to suggest the diagnosis of ichthyosis hystrix.

DR. HOWARD J. PARKHURST, Cleveland: I should like to know why these cases should be classified as ones of ichthyosis hystrix when the intervening skin is normal and shows no evidence of ichthyosis.

DR. E. W. NETHERTON, Cleveland: I do not believe that one always has to have ichthyosis of the ordinary type associated with history of ichthyosis.

DR. JOHN A. GAMMEL, Cleveland: I thought that this patient's case closely resembled the cases reported by Dr. Morris Waisman and Dr. Hamilton Montgomery (ARCH. DERMAT. & SYPH. **45**:259-282 [Feb.] 1942). The histologic picture concurs with their description.

Xeroderma Pigmentosum with Precocious Malignancy. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

L. K., a boy aged 3½ years, presents an eruption which began when he was 19 months of age. The family history shows no consanguinity of the parents. There are three sisters, who are well. There has been no similar eruption in the family or either parent.

The mother states that when this child was 19 months of age "freckles" began to develop on the face. The child played in the sunshine without any protection. During the past year numerous small hyperpigmented spots have developed on the face, neck and exposed portions of the chest and arms. Likewise, small hyperkeratotic papules, filiform warts and crusted lesions have developed. Some of the crusted lesions have healed, leaving pinkish white scars. Five weeks ago, a tumor appeared on the left ala of the nose. The lesion has grown rapidly and has become covered with an adherent hemorrhagic crust. More recently, smaller crusted lesions have appeared below the right eye.

There is an eruption limited to face, neck, upper portion of chest, arms and exposed portions of the legs. It consists of numerous small pigmentations, small keratotic papules and filiform keratoses and scattered pink scars. There are a few telangiectases on the scarred areas. There is a large nodule on the left side of the nose. This involves the nasolabial fold and is covered with an adherent hemorrhagic crust. There are irregular crusted areas on the right side of the face.

DISCUSSION

DR. HARLEY A. HAYNES JR., Akron, Ohio: I think that this is a typical case and unusual in both the severity and the precocity of the epithelioma. In 1936 I reported a case of xeroderma pigmentosum with multiple malignant lesions in a boy 3 years and 10 months old. At that time this patient was the youngest of which I could find record.

DR. HAROLD N. COLE, Cleveland: I have had a case of this type—that of a girl who was about 1½ years old when I first saw her and who is now 27. She has been treated for at least forty to fifty epitheliomas of the face and hands. She keeps out of the light except mornings or evenings and always wears a hat with a red lining. She uses 10 per cent phenyl salicylate in yellow petrolatum, which acts as a protection against ultraviolet radiation.

DR. FREDERICK M. JACOB, Pittsburgh: The mother says that a good many of the epitheliomas rub off of their own accord. I have removed about five from a girl at home. There is skin grafted on almost the entire forehead. The grafted skin looks normal, and xeroderma pigmentosum does not seem to have developed in it.

DR. ROBERT C. JAMIESON, Detroit: The mother mentioned, on questioning, that this boy is one of four and the only one to have the lesions. In his early life he was rather sickly and was exposed almost constantly to the sun. I wonder whether this disease is a result of exposure to the sun or ultraviolet rays.

DR. MYER W. RUBENSTEIN, Pittsburgh: I do not think so. In this particular instance, it is interesting to note that there are no lesions on the lower extremities at all. With reference to the use of radiation: The boy had several lesions on the back of his neck, and they dropped off spontaneously; hence I do not give too much credit to roentgen rays. I think that the boy's outlook will be best if he will keep himself absolutely out of the sunlight. However, this can be done, as he can sleep in the day and work at night.

Adenoma Sebaceum (Pringle Type Forme Fruste). Presented by DR. DONALD N. MACVICAR, for DR. HAROLD N. COLE and DR. JAMES R. DRIVER.

J. C., a white boy aged 7 months, was seen because of several growths on the toes. When he was 3 days old, a small swelling was noted on the left middle toe. This lesion persisted and increased slowly in size. A similar swelling developed on the right middle toe and has slowly increased in size. Mental and physical development have been normal. There is no family history of cutaneous disease or epilepsy.

The child seems alert and is of normal physical development, except for the toes. There is a firm raised dull red tumor involving the dorsum and medial surface of the left middle toe. Similar, but smaller, lesions are present on the right middle and right second digits. The skin of the face is normal.

Roentgenograms of the feet revealed no abnormality of the bony structure.

Histologic examination of a piece of tissue removed from one of the lesions revealed a moderate degree of parakeratosis of the epidermis. The granular layer was well developed. The rest of the epithelium was normal. The tissue beneath the epidermis consisted of interlacing bundles and strands of loose fibrous tissue. Many nuclei were present, and some of the cells presented a vacuolated, almost foamy, appearance of the cytoplasm.

DISCUSSION

DR. HARLEY A. HAYNES JR., Akron, Ohio: I disagree with the diagnosis of adenoma sebaceum because I believe that neither the clinical picture nor the histologic structure points to that. I am not ready to offer another diagnosis, except that of a congenital defect.

DR. HOWARD J. PARKHURST, Toledo, Ohio: In the disease described by Pringle, I believe, the adenoma sebaceum on the face was accompanied with subungual fibromas. It would be interesting to follow this case to see whether an adenoma sebaceum develops on the face.

DR. HAROLD N. COLE, Cleveland: The baby presents these unusual subungual growths on the toes—histologically fibromas in type. There are no lesions on the rest of the skin. The child is thus far perfectly alert and apparently normal. Nevertheless, I am not aware of any congenital defect producing this picture. A forme fruste of Pringle's adenoma sebaceum seems to be the best explanation. As Dr. Parkhurst says, we are going to follow this baby. There may be mental deficiencies later. It is a remarkable case in my estimation.

A Case for Diagnosis (Periarteritis Nodosa?). Presented by DR. DON R. PRINTZ and DR. SAM AYRES III.

J. F., a white man aged 69, complains of a generalized eruption of three years' duration characterized by exacerbations and remissions. The present episode started nine months ago with low grade fever, general malaise, loss of weight and generalized muscular tenderness. The lesions have been pruritic in recent months. The patient gives no history of allergy or ingestion of drugs. His general health in the past has been good.

He presents a generalized eruption which is papular to nodular in character; the lesions average about 0.5 cm. in diameter. The primary lesion is an erythematous papule which extends into the subcutaneous tissue and acquires a yellow pustular appearance. However, repeated lancing of the papules reveals no purulent content, only a thin serous material and bright red blood. The papules regress, leaving a light brownish pigmented area. Similar lesions have appeared on the buccal mucosa and pharynx. The lymph nodes are not abnormal. There are discrete freely movable nodules on the arms and abdomen. The liver is palpable about 2 fingerbreadths below the right costal margin. The heart is not enlarged, but a systolic murmur is present over the entire precordium. Blood pressure is 110 systolic and 50 diastolic. There are rales in the bases of both pulmonary fields and slight pitting edema of both legs, more pronounced in the right.

The urine was normal. The hemogram revealed 6 Gm. of hemoglobin per hundred cubic centimeters of blood, 1,640,000 erythrocytes and 4,150 leukocytes, with 2 per cent eosinophils, 66 per cent polymorphonuclear neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 8 per cent unknown. Studies of smears showed the bone marrow to be normal. Aerobic and anaerobic cultures of blood, cutaneous lesion and bone marrow were negative for bacteria and fungi. A typical cutaneous lesion processed and injected into a guinea pig gave no evidence of disease at autopsy. Results of determinations of concentrations of bromides and iodides in the blood and urine were within normal limits. Chemical examination of the blood revealed 130 mg. of sugar, 118 mg. of cholesterol and 14.7 mg. of urea nitrogen per hundred cubic centimeters of blood. The sedimentation rate was rapid. Total protein was 6.3 Gm., albumin 3.5 Gm. and globulin 2.8 Gm. Kline reactions of the blood for syphilis were normal. Roentgenograms of the lungs and heart showed no parenchymal involvement of the lungs. However, there was an abnormal prominence at the right hilus which was probably due to blood vessels rather than to lymph nodes. The intradermal tuberculin test with purified protein derivative (dilution 2) revealed 2 cm. of induration in forty-eight hours. The results of agglutination tests for Brucella, Proteus X_{19} and typhoid and paratyphoid A and B organisms have been negative.

Microscopic examination of a typical cutaneous lesion revealed a normal epidermal layer with no hyperkeratosis. The papillary layers and superficial corium were edematous. In the superficial portion of the corium and extending deeply in a perivascular distribution was an inflammatory reaction which was characterized by edema and an infiltration of polymorphonuclear cells and lymphocytes. The cellular exudate showed necrosis

with fragmentation of fibroblasts forming large stellate cells which were occasionally in whorls grouped around capillary spaces. Histologic examination of a subcutaneous nodule from the right forearm showed a collection of fat with little supporting tissue and vessels. A section of bone marrow was about 95 per cent hemapoietic material and the remainder fat. A normal distribution of cells was seen with the usual predominance of myeloid elements. A smear of bone marrow showed a normal cytologic picture with an occasional blast form but not in sufficient numbers to indicate a pathologic process.

Treatment has consisted of repeated transfusions of whole blood and a thorough trial of sodium salicylate and sulfathiazole. There has been no change in the patient's general condition or cutaneous manifestations.

DISCUSSION

DR. HERBERT H. BAUCKUS, Buffalo: There are a variety of lesions on this man; therefore I think that the diagnosis is open to question. On the left side of the trunk I felt two distinct nodules in the skin, and I suspect the picture of Hodgkin's disease might appear.

DR. LOREN W. SHAFFER, Detroit: There are unusual features in this case. The picture is that of an apparent background of toxemia and severe anemia, which would go with a toxic eruption. I should not expect to find the blood picture which the patient has in a person with Hodgkin's disease. By saying the "blood picture," I mean the anemia more than the differential count.

DR. HAROLD N. COLE, Cleveland: This patient has been under observation off and on for the last three or four years, and he has at various times been hospitalized because of the severity of his disease. He has had many transfusions. At no time have blood cultures been positive. At no time has the blood picture suggested lymphoblastoma. Lymph nodes have been taken out and sternal punctures made, but we have been unable to arrive at the diagnosis of lymphoblastoma. On the other hand, we are dealing with a systemic process which comes and goes. The temperature changes suggest Hodgkin's disease. He will get better and go along for a while and will then come back again looking and feeling much the same as he is now. Many of the tumors are subcutaneous and will come up to the surface and will break, and he will scratch them open. After studying the whole situation we did not think of any disease that would fit into this picture other than periarteritis nodosa. As everybody can see now, he is a sick man. He is seriously anemic, and unless more transfusions are given to him he may not live long. He probably has the same sort of nodules in the internal organs.

CLEVELAND DERMATOLOGICAL SOCIETY

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May 25, 1944

Herpes Simplex Resembling Herpes Zoster. Presented by DR. BENJAMIN LEVINE.

D. H. is a white woman aged 31. Her mother is living and well, but her father died of tuberculosis. Two brothers are living and well, but one sister died of spinal meningitis.

At the age of 7 years she had a severe attack of influenza. After the attack of influenza, "cold sores" developed. They recurred always in the same locations, either on the right side of the nose or on the right cheek. Sometimes an attack would be precipitated by excessive exposure to the sun and on other occasions would appear for no apparent reason. Since she was 7 years old, she has had almost two score attacks of herpes. The last attack, which began on May 17, 1944, was ushered in with localized pain, generalized malaise and some febrile reaction. It is by far the severest and the most extensive eruption which she has had. The patient complains of burning and smarting of both eyes, and yet there are no visible lesions. Examination shows lesions on the anterior and right side of the nose and the right malar region. There are numerous groups of vesicles that are almost confluent. There are several little groups of vesicles in the right malar region laterally and in the central part of the forehead.

Treatment has consisted of intravenous injection of 10 cc. of 10 per cent aqueous solution of sodium iodide on May 20 and May 24. She refused serial vaccinations with cowpox vaccine.

DISCUSSION

DR. JOHN A. GAMMEL: I think that the history of frequent recurrences rules out herpes zoster. The attacks come on about every six months or so, and this frequency is common with herpes simplex. I suggest therapeutic smallpox vaccine or moccasin venom. I have had fair success with both of them.

DR. BENJAMIN LEVINE: I saw this patient for the first time four or five days ago. The lesions looked like typical herpes zoster, with the close grouping of the vesicles and the wide extent of the lesions and their distribution. The lesions slightly overlapped the midline in the same way that the nerve fibers overlap. Also their keeping completely to one side of the face suggested herpes zoster. Because of the history, however, I called the disease herpes simplex instead of herpes zoster. It presented that particular problem of diagnosis.

DR. HUGO HECHT: This is an unusual case. Herpes simplex seldom presents more than fifteen or twenty small vesicles, all at the same time and all of the same size. Rarely more than 20. I do not see why herpes zoster could not be considered. I think that there must be an irritation in the center of the nerve. It is always located in the same place, on the right side of the face; hence the maxillary nerve which is involved. I think that it would be interesting to send the patient to a neurologist to see whether there is something wrong. I think that the disease is herpes zoster and not herpes simplex. The two diseases are related, as both are caused by a virus. Herpes zoster is an infection of the ends of the nerves.

DR. BENJAMIN LEVINE: The lesions in previous attacks have been more like those of herpes simplex—sharply defined and limited. On this occasion the lesion looked like one of herpes zoster. Previously the disease may have been nothing but herpes simplex, but on this occasion it was herpes zoster.

Folliculitis Keloidalis. Presented by DR. BENJAMIN LEVINE.

L. S., a Negro aged 32, is a service station attendant. He had stomach trouble as a child and has recently been discharged from the Army because of gastric ulcers. He acquired syphilis in 1929. The serologic reaction was negative when he entered the Army in November 1942.

In 1935 pimples appeared on the back of the neck and have persisted. Eventually a large part of the scalp was involved. The occipital portion of the scalp and the nape of the neck are studded with numerous pinhead to split pea–sized tumors of keloidal type, which are smooth and shiny. The occipitoparietal regions are covered with a dark chamois-colored tumor mass that is confluent and ridged longitudinally. There were some pruritus and soreness. The Kline exclusion reaction was negative.

Histologic study revealed granulation tissue in the dermis and subcutaneous areas. There were scattered giant cells and some structures suggesting degenerated hairs in the granulation tissue. In two sections the granulation tissue lined a small defect. At some distance from the cellulitis and sinus, there were scarring and round cell infiltration about cutaneous glands and hair follicles. In the region of the former the epidermis was elevated. There was abundant brown pigment in the basal layer of the epidermis.

The treatment consisted of roentgen radiation to the occiput, four doses of 100 r each, filtered through 1 mm. of aluminum.

DISCUSSION

DR. GEORGE W. BINKLEY: Was low voltage roentgen irradiation the only therapy administered?

DR. BENJAMIN LEVINE: Yes. I think that the therapeutic results have been good. One small patch has escaped the rays on one side, and some of these untreated lesions seem to be much larger.

DR. JAMES R. DRIVER: Sometimes solid carbon dioxide is of value in treating this disease.

Recurrent Urticaria Chronica. Presented by DR. HUGO HECHT.

J. C., a white man aged 34, is a teacher. After a tuberculous infection of the lungs, a thoracotomy was performed in 1937. Further treatment was taken in a sanatorium with pneumothorax. The tuberculosis is now under control. Four years after the aforementioned thoracotomy, an itching eruption appeared on the right upper quadrant of the abdomen and spread slowly over the body with alternating intensity. Cool weather is favorable for the patient. There is little itching.

When the patient was first seen, the scalp, face, back and palms were free from lesions. Many lesions are located on the neck, arms, abdomen, hips, buttocks, thighs and legs. Some lesions are visible on the soles. Each lesion is completely isolated; there is never confluence of single lesions, but often there are groups of lesions in certain regions, e. g., the right upper quadrant of the abdomen. After days or weeks they disappear slowly, leaving light brown pigmentation. New lesions return at the site of the former ones. They are always the same size, 0.5 cm. in diameter. The new lesion is elevated, usually oblong and yellowish red and never vesicular and never surrounded by a white zone. A few lesions are covered with a crust. These never open spontaneously, but the patient rubs them open after a bath.

The Kline exclusion reaction was negative. Urinalysis showed a 2 plus reduction of Benedict's solution. Examination of the blood for sugar showed 75 mg. per hundred cubic centimeters. Tests of the urine for sugar were made from time to time, but they never showed more than a trace.

Histologic examination showed a somewhat thickened epidermis. There was some infiltration by wandering cells. The upper part of the dermis showed some edema and moderate to considerable round cell infiltration, lymphocytes and larger mononuclears predominating. In the thickened epidermis the rete cells were swollen in places, and the nuclei were larger than average. The basement membrane in many places was poorly defined. There was round cell infiltration in the upper part of the dermis, about the vessels associated with cutaneous glands and hair follicles. There was also some infiltration of the epithelium of hair follicles and of sudoriferous glands. In places numerous polymorphonuclear leukocytes were seen, although mononuclear cells predominated. Scattered throughout the infiltrate were large mononuclear cells which resembled mast cells.

External treatment with low voltage roentgen rays, ultraviolet rays from a hot quartz mercury vapor lamp and ointments resulted in no lasting improvement. Other ineffective internal treatments were an acid ash diet, then alkaline ash foods, thyroid extract and calcium and arsenical medication. A temporary improvement after twelve injections of the patient's blood could not be duplicated with a second series of injections.

DISCUSSION

DR. GEORGE W. BINKLEY: The clinical aspects that detract from a diagnosis of urticaria pigmentosa are the onset of the disease in adult life, the absence of whealing and dermographism and the slight amount of pigmentation. Some of the histologic features were similar to those of urticaria pigmentosa, but the changes were not pathognomonic. There was an increase in pigment in the basal layer. The dense infiltrate in the entire corium was made up of monocytes and a few giant cells. In the short time available for study, I was uncertain as to the presence of mast cells.

DR. EUGENE C. STERN: I think that the pigmentation could be explained by the ultraviolet rays which were given. The skin is tanned where the patient received ultraviolet radiation and is not tanned where he did not receive this treatment.

DR. HUGO HECHT: If one accepts the existence of urticaria pigmentosa without mast cells, then this is a case of urticaria pigmentosa. The first biopsy specimen was taken before the patient was treated. There were big clusters of mast cells, consistent with the diagnosis of urticaria pigmentosa. In the biopsy specimen taken before the ultraviolet ray treatment there were no chromocytes; hence I think that Dr. Stern's suggestion is correct. The second possibility is allergy. I showed the slide to Dr. Benjamin S. Kline, pathologist. He said that the disease is definitely not an allergy. I not only made patch tests, but I gave the patient elimination diets. For four months he ingested an alkaline diet and for four months an acid diet. Nothing happened. I found that twelve injections of his own blood was the best treatment, but when I tried it the second time the disease became worse. The patient had active pulmonary tuberculosis at one time. He still has a mild infection of the lungs. The cutaneous lesions come always in the same places, three or four times a year. The disease is a cutaneous reaction which flares suddenly. I think that it is an urticaria chronica caused by toxins from his tuberculosis, which irritate the sensitized skin.

Granuloma Annulare. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

W. S., a white man aged 56, has had a nonpruritic papular eruption on his extremities for one year. The lesions appeared first on the wrists and then, in rapid succession, involved the dorsa of the hands, the elbows and the lower extremities.

He has been receiving injections of liver extract from his local physician for seven months without much benefit. He was taking no medicine prior to the onset of his eruption. He has had no roentgenotherapy. There is no family history of tuberculosis.

The eruption consists of flat angular brownish and yellowish red closely grouped papules, 2 mm. in diameter. These cover the dorsa of the hands and the extensor surfaces of the forearms and are seen in smaller groups on the wrists, flexor surfaces of the forearms and thighs. Many of the papules are arranged in the form of small annular plaques. The skin on the dorsa of the hands appears to be slightly atrophic. Diascopic examination shows an apple-jelly-like deposit in most of the papules. Many of the lesions near the site from which the biopsy specimen was taken have disappeared.

The remainder of the physical examination reveals normal conditions.

The hemogram, blood sugar and urine were normal. The Wassermann and Kahn reactions of the blood were negative. The blood cholesterol level was 217 mg. per hundred cubic centimeters. Tuberculin in a 1:5,000 dilution elicited a positive reaction. A roentgenogram of the chest revealed normal conditions.

Histologic examination of portions of the plaques from the right elbow and forearm revealed a normal epidermis, except for slight cribriform hyperkeratosis. The papillary layer was uninvolved. There was extensive focal perivascular inflammation of the corium, with decided thickening of the endothelium of the blood vessels. The focal infiltrate consisted of a reticulum of stellate cells, with a sparse infiltrate of lymphocytes. A few of the stellate cells were enlarged and had finely vacular eosinophilic cytoplasm.

DISCUSSION

DR. JOHN A. GAMMEL: The eruption does not look like any granuloma annulare I have seen, and I have not seen granuloma annulare in a person of this patient's age.

DR. BENJAMIN P. PERSKY: I think that on the flexor surfaces of the wrists this man shows lesions which are somewhat suggestive clinically of granuloma annulare. He has received some roentgen ray therapy, which may have altered the original appearance of the lesions, inasmuch as granuloma annulare is a relatively radiosensitive lesion. I believe that the slide shows changes which might be considered consistent with granuloma annulare. There is a granular bluish discoloration to the connective tissue in some areas—a basophilic degeneration. There are also seen some scattered epithelioid cells with a banal infiltrate interspersed among them. Histologically, the lesion could be considered granuloma annulare, although it is not clinically typical.

DR. JAMES R. DRIVER: While clinically and also histologically the lesions are not typical, I favor the diagnosis as presented.

DR. W. R. HUBLER: Dr. Fred Wise presented a 16 year old girl with granuloma annulare before the Manhattan Dermatologic Society in 1939 (ARCH. DERMAT. & SYPH. **40**:291 [Aug.] 1939). She had typical lesions on the hands, except that the central portions of the annular plaques were covered with pinhead-sized papules. Similar small flesh-colored papules were also scattered over the body. The latter lesions, he said, were not uncommon, especially in children. The histologic picture of one of the typical plaques on the hand was that of perivasculitis. Dr. Satenstein commented that there are many clinically typical cases of granuloma annulare in which only vascular reaction is shown histologically. In a discussion at the New York Academy of Medicine in 1929 (ARCH. DERMAT. & SYPH. **19**:495 [March] 1929), Dr. Howard Fox described a case from Dr. Goldenberg's service at Mount Sinai Hospital, in New York, in which the patient had a more or less generalized eruption made up of small papules, which, according to Dr. Fox, almost any dermatologist would call lichen planus. In this case, the biopsy specimen was typical of granuloma annulare. At first glance, our case might also be taken for one of lichen planus. The lesions around the site of the biopsy specimen have disappeared during the past week. As far as age is concerned, many cases of typical granuloma annulare in adults have been reported.

METROPOLITAN DERMATOLOGICAL SOCIETY

ROYAL M. MONTGOMERY, M.D., *President*

JAMES LOWRY MILLER, M.D., *Secretary*

May 15, 1944

A Case for Diagnosis (Allergic Eruption?). Presented by DR. THOMAS N. GRAHAM.

H. D., a white man aged 68, was first seen by me on Feb. 28, 1944. He complained of a generalized itching eruption of two months' duration. There was no history of ingestion of drugs or of allergy.

There were numerous erythematous, papular, discrete and confluent lesions, many of which presented a distinctly urticarial appearance. General physical examination showed only dental caries. The Wassermann reaction of the blood was negative. Dental roentgenograms showed abscessed teeth. The urine was essentially normal.

After removal of the infected teeth, the eruption flared up slightly and then practically disappeared, but only for about two weeks. Subsequent therapy with calcium, dilute hydrochloric acid and elimination diets failed to produce any appreciable improvement. Within the past few weeks a few of the lesions have become scaly and somewhat resemble psoriasis guttata. Above the wrists and ankles there have recently appeared a few hemorrhagic macules.

DISCUSSION

DR. LAIRD S. VAN DYCK: The color and distribution of the scaly papules suggest parapsoriasis, but the severe itching in a man of that age always makes one suspicious that the disease may be mycosis fungoides. A histologic report should help one to make the diagnosis.

DR. JOSEPH C. AMERSBACH: Some of the lesions on the wrist resembled lichen planus. On closer observation other lesions appeared to be infiltrated and scaling. The patient also had lesions of the scalp, and so I think that the disease may be parapsoriasis, psoriasis or lichen planus.

DR. GERALD F. MACHACEK: I have nothing to add. He has no lesion in the mouth.

DR. J. LOWRY MILLER: I believe that further observation and study of this patient will establish the diagnosis of a disease of the lymphoblastoma group. I suggest biopsy of a lymph node, studies of the blood and a roentgenogram of the chest.

DR. ROYAL M. MONTGOMERY: From questioning it is evident that this patient does not take a normal amount of vitamin C in his diet. I suggest giving him 300 mg. of ascorbic acid daily and observing the results. Vitamin C deficiency modifies the configuration of the lesions.

DR. RICHARD J. KELLY: I favor a diagnosis first of parapsoriasis and second of lichen planus.

DR. MAX WOLF (by invitation): I favor the diagnosis of parapsoriasis. The widespread distribution of small papular and macular scaly lesions over extended areas of the surface would correspond to the clinical picture of pityriasis lichenoides chronica or parapsoriasis.

DR. THOMAS N. GRAHAM: I do not think lymphoblastoma a probable diagnosis in this case. The eruption so nearly disappeared at one time that only a few lesions were slightly perceptible. This occurred within a period of a few days. At times the lesions have appeared as typical wheals. A biopsy is apparently necessary to establish a diagnosis.

DR. J. LOWRY MILLER: The spontaneous remission noted in this patient previously does not rule out lymphoblastoma. I have under observation now a patient with mycosis fungoides whose lesions come and go without treatment.

NOTE.—A subsequent blood count showed 4,800,000 erythrocytes and 8,400 leukocytes per cubic millimeter. The hemoglobin amounted to 13.1 Gm. per hundred cubic centimeters. The differential blood count showed 71 per cent neutrophils, 27 per cent lymphocytes and 2 per cent mononuclear leukocytes. A biopsy specimen showed chronic eczema with lichenification. There was no evidence of lymphoblastoma, lichen planus or psoriasis.

Alopecia Prematura. Presented by DR. LAIRD S. VAN DYCK.

A. C., a 16 year old girl, the daughter of an Italian physician, has a diffuse thinning of the hair of the scalp, which began five months ago. She has had no illness for the past few years, but she was struck by an automobile two years ago, receiving an injury to the head which rendered her unconscious at the time. For two or three years previous to the onset of the rapid loss of hair, she had a thick scaly eruption on the scalp which she cured with a "dandruff cure" suggested by a neighbor. Shortly after this she noticed that her hair was falling out more rapidly each day.

The scalp shows no inflammation or scaling. There is a diffuse thinning of the hair, especially over the vertex. The remaining hair seems abnormally dry, and her nails are brittle.

DISSCUSSION

DR. JOSEPH C. AMERSBACH: I think that this case presents a difficult problem. There is the possibility that a girl of this age may have a regrowth of the hair which she has lost. One certainly has to consider the part emotion plays in this condition, which is undoubtedly dependent on thyroid function.

DR. J. LOWRY MILLER: I feel that the alopecia in this patient is due to a disturbance in the functioning of the thyroid gland. The thyroid mechanism was probably adversely affected by the emotional upset. I suggest thyroid therapy unless the basal metabolic rate is definitely increased, but I do not expect that it is.

DR. RICHARD J. KELLY: This patient should have a thorough medical examination with special attention to the thyroid.

DR. THOMAS N. GRAHAM: I agree with what has been said in regard to this case. One must consider an infectious process, possibly a low grade staphylococcic infection of the scalp. I believe that there are atrophy and scarring.

DR. ROYAL M. MONTGOMERY: There is scarring present. For that reason the results from any type of therapy would be questionable. She was given injections of chorionic gonadotropin, a substance which used to be given for alopecia, but it is my opinion that it produced few satisfactory results.

DR. LAIRD S. VAN DYCK: I do not have much to add, except that I share the opinion about chorionic gonadotropin as far as growth of hair is concerned. I have given it to patients for six to twelve months without beneficial results. She has abnormally dry skin; her nails are brittle, and her general appearance indicates some endocrine disturbance.

Tinea Ciliorum and Tinea Corporis. Presented by DR. ROYAL M. MONTGOMERY.

F. E., a girl aged 9 years, has had cutaneous lesions for the past six weeks. When she came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 18, she had a circinate papule the size of a 25 cent piece with peripheral scaling and central involution on the nape of the neck. She also had a small patch on the right calf and on the right upper eyelid. On examination under ultraviolet rays with a Wood filter a number of eyelashes fluoresced on the right upper eyelid. The eyelashes and scales from the neck were cultured and yielded Microsporon audouini. Her sister has tinea capitis caused by M. audouini.

At present the patient's cutaneous lesions are much improved, and only slight scaling is present. The upper eyelid is also normal, with no inflammation about the hair follicles. Fluorescent hairs are present. The scalp is normal.

DISSCUSSION

DR. RICHARD J. KELLY: This case was very interesting. I have never seen one like it before. I agree with the diagnosis.

DR. LAIRD S. VAN DYCK: I want to compliment the man who made the diagnosis of the lesion of the eyelid.

DR. ROYAL M. MONTGOMERY: In the previous case which I reported (ARCH. DERMAT. & SYPH. **46**:40 [July] 1942), also caused by M. audouini, a pustular folliculitis developed and the eyelashes were spontaneously epilated. There is still activity in the eyelashes in this case, in spite of manual epilation and the application of medication.

A Case for Diagnosis (Alopecia Areata; Arsenical Dermatitis?). Presented by DR. J. LOWRY MILLER.

W. W., a Negro boy aged 7 years, was admitted to the Vanderbilt Clinic on Aug. 13, 1943, complaining of total loss of hair around the sides and back of the head and dermatitis involving most of the body. The dermatitis had had exacerbations and remissions over a period of two and one half years. There had been loss of hair around the sides and back of the head, with a normal sharply marginated growth of hair on the top of the scalp. The dermatitis cleared with the use of a juniper tar salve, but the alopecia remained. A few scattered plugged follicles were seen, but no scarring was noted.

An examination of the blood for arsenic showed 0.22 mg. of arsenic per 100 Gm. of dry blood. The Wassermann reaction of the blood was negative. A biopsy specimen from the arm showed a psoriasiform dermatitis. Mental tests showed a mental age of 2

years, an intelligence quotient of 40 and decided mental retardation.

DISSCUSSION

DR. LAIRD S. VAN DYCK: I notice in bald areas on both sides of the scalp acuminate follicular papules such as one finds in Graham Little's syndrome. I do not see how one can classify this as a case of alopecia areata. It must be a rare form of congenital alopecia.

DR. GERALD F. MACHACEK: I remember that the child had a severe pyoderma.

DR. THOMAS N. GRAHAM: I agree with Dr. Van Dyck. I think that the disease is congenital.

Sarcoid. Presented by DR. J. LOWRY MILLER.

M. L., a Negro woman aged 36, was first seen at the Vanderbilt Clinic, on April 12, 1944, complaining of lumps on the eyelids, arms and legs of two and one-half years' duration. In her past and family histories there was no mention of tuberculosis or syphilis. She was born in the city of New York. Her present trouble began with a lump forming under the skin of the left arm. A specimen for biopsy was taken from this lump. Gradually new lumps have appeared. Her general health has been good.

Examination shows about eight red oval-shaped nodules, the size of a pinhead to that of a pea, which on diascopic pressure show gray foci situated on the eyelids, upper lip and ala nasi. On the left arm and forearm are two half-dollar sized red indurated scarred (from biopsy) areas. On the lower extremities are four or five nodules as large as and even larger than a marble, movable under the skin and underlying tissues. The overlying skin is normal in appearance. The tip of the right middle finger is red, slightly tender and swollen.

General physical examination showed nothing abnormal. The blood count was normal, and the Wassermann reaction of the blood was negative. A tuberculin test (1:1,000) elicited a negative reaction. A roentgenogram of the chest showed essentially normal conditions. A biopsy showed tuberculosis cutis of the sarcoid type.

DISSCUSSION

DR. GERALD F. MACHACEK: The diagnosis has been substantiated by biopsy.

Psoriasis. Presented by DR. J. LOWRY MILLER.

W. B., a Negro housewife aged 54, was admitted to the Welfare Island Dispensary on April 18, 1944, complaining of itching patches of three years' duration on the right leg and right forearm. She stated that a routine Wassermann test in 1929 elicited a positive reaction. She received three courses of ten injections each of neoarsphenamine and three courses of a bismuth preparation, after which she had a hysterectomy for fibroids. Five Wassermann tests during the past few years have all elicited negative reactions. She has received one course of injections in her arm and one in her hip in the past year. She says that she has taken no medicines by mouth. Her general health has been good.

Examination shows two palm-sized and two dime-sized patches situated on the right shin. A quarter-sized similar lesion is present on the right forearm. The lesions are sharply marginated with a threadlike red elevated margin running along the entire periphery of the lesion. The center of the lesion is violaceous and studded with whitish dots. There is no evidence of scarring. Mucous membranes of the mouth are clear.

Histologic examination showed an inflammatory lesion of a psoriasiform character.

DISCUSSION

DR. THOMAS N. GRAHAM: I think that clinically the eruption does not look like psoriasis.

DR. LAIRD S. VAN DYCK: One feature which militates against the diagnosis of psoriasis is the depression of the central portion of the larger patch below the level of the surrounding skin. However, the scaling at the border is characteristic of psoriasis.

DR. JOSEPH C. AMERSBACH: I suggest further observation of the case and biopsy at a future date.

DR. ROYAL M. MONTGOMERY: I agree with the diagnosis of psoriasis. I have seen several Negroes with this disease. Dr. Howard Fox reported on this subject. The scaling around the border is typical of psoriasis, but the typical micaceous scaling is not present. The pigmentation in Negroes produces a clinical appearance different from that in white patients.

DR. MAX WOLF (by invitation): The patient presented in the beginning two separate large lesions covering nearly the entire anterior aspect of the right leg and two smaller lesions on the ankle. The patches had a definite bluish violaceous color and a slowly progressive raised inflammatory border with partly polycyclic outlines. Throughout the center of the lesions there were tiny "blisters," which disappeared after application of boric acid ointment, but flaky scales remained. Because of the purplish hue and the raised polycyclic border I thought of annular lichen planus. The microscopic evidences of psoriasiform changes are not corroborated by the clinical appearance of the lesions.

DR. J. LOWRY MILLER: I suppose the diagnosis of psoriasis should be accepted because of histologic changes. Clinically the case is puzzling. I thought even of amyloidosis because of pinhead-sized foci all through the lesions.

Pediculosis of the Eyelashes. Presented by DR. J. LOWRY MILLER.

J. H., a Negro boy aged 9 years, presented himself at the Welfare Island Dispensary, complaining of itching of the eyelids of one week's duration. Examination showed nits and pediculi in the eyelashes.

DISCUSSION

DR. RICHARD J. KELLY: I am interested in the case because of the child's age. Yellow mercuric oxide is indicated.

DR. JOSEPH C. AMERSBACH: The disease is of unusual interest because of the single area affected and its location. The use of a mild antiseptic ointment, such as 0.25 per cent yellow mercuric oxide, I believe, is adequate in this case.

DR. GERALD F. MACHACEK: I have seen pediculosis of the eyelashes in children, evidently due to crab lice. The therapy has been described adequately.

News and Comment

ELIGIBILITY REQUIREMENTS FOR EXAMINATION BY THE AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY, INC.

I. General Requirements.

1. High ethical and professional standing.
2. Graduation from a medical school recognized by the Council on Medical Education and Hospitals of the American Medical Association.
3. Satisfactory completion of an internship of not less than one year in a hospital approved by the same Council or its equivalent in the opinion of the Board.
4. A license to practice medicine.
5. Membership in the American Medical Association or membership in a similar society recognized as having the same purpose as the American Medical Association.
6. Citizenship in the United States or citizenship —meaning native citizens—in Canada or Cuba.

II. Special Requirements.

Applicants for certification by the Board are classed in two groups as follows:

Group A consists of physicians who have limited their practice mainly to dermatology and syphilology for ten or more years, including a period of training satisfactory to the Board.

Group B consists of physicians who have completed an approved three year period of training.

In accordance with the program recommended to the various specialty boards by the Advisory Board for Medical Specialties, the following minimum requirements of special training for admission to examination have been established:

A period of study, after the internship, of not less than three years. This training may be obtained as resident, fellow or graduate student in clinics, dispensaries, hospitals or laboratories recognized by the Council on Medical Education and Hospitals of the American Medical Association and approved by the American Board of Dermatology and Syphilology as competent to provide a satisfactory training in dermatology and syphilology. This period of specialized training shall include:

(*a*) Graduate training in the basic medical sciences which are necessary for the proper understanding and treatment of the diseases involved in this specialty.

Instruction in the following fundamental subjects as related to the skin is deemed advisable by the Board: embryology, histology, chemistry, physiology, bacteriology, mycology, parasitology, pathology, immunology, serology, pharmacology and materia medica and physics of physical therapy.

(*b*) Carefully supervised clinical and laboratory experience in the specialty.

(*c*) Annual examinations in the clinical, laboratory and public health aspects of dermatology and syphilology.

Candidates who plan to take part of their training under the supervision of a specialist certified by the Board should also be certain that he has been accepted as a preceptor of the Board. Time spent with an unqualified instructor may count only as experience and not as training.

III. Credit for Work in the Armed Forces.

In view of the widespread interest in specialization in dermatology by men who are or have been in service, the American Board of Dermatology and Syphilology has drawn up an outline to cover in a broad way the credits allowed toward training and experience of candidates for their military work. In view of the variability of dermatologic work and the differing conditions under which it was carried on by commissioned medical officers of the Army, Navy and Public Health Service, the Board is unable to issue specifications for eligibility for examination to cover every situation that has arisen in the experience of every candidate, but the following general statements can be made:

1. Full credit will be given for dermatologic training in approved institutions, which preceded the military service.

2. Full time dermatologic military service may be credited, at the discretion of the Board, for part, or in some cases all, of two years of the three required years of *training*. But at least one year of the three years' required training, to include instruction in the fundamental subjects deemed essential for an adequate dermatologic education, must be spent in one of the institutions approved for a three year training program by the Board and by the Council on Medical Education and Hospitals of the American Medical Association.

3. In any event, the Board strongly urges that the candidate supplement his military experiences by a further period of systematic and supervised dermatologic training before the examination.

4. A credit for one year as *experience* has also been voted by the Board for one year of any military service. Thus a medical officer who passes the examination at the end of three years of training will receive his certificate one year later instead of at the completion of a total of five years' training and experience. Dermatologic work while in the armed forces, not credited as training, may satisfy part or all of the remaining year of required dermatologic experience.

5. For commissioned officers the total fee will be $50 instead of $75; of this, $25 must accompany the application. The examination fee of $25 is payable when the candidate is notified that his application has been approved by the Board. These fees are not returnable.

In order that a prospective candidate may ascertain the credit he will receive for his military service, it will be necessary for him to fill out a special form which may be obtained from the Secretary.

Dearth of Opportunities for Training

The present greatly increased demand for training by recently discharged veterans has created a dearth of opportunities in accredited institutions.

It is possible that there are other institutions which can qualify to train suitable applicants at least partially. It is also undeniable that many capable teachers have not as yet applied to be preceptors so that they will also be available to supervise part of the training of promising candidates.

For further information apply to the secretary, Dr. George M. Lewis, 66 East Sixty-Sixth Street, New York 21.

GENERAL NEWS

Section on Dermatology and Syphilology, American Medical Association.—Applications for places on the program of the Section on Dermatology and Syphilology at the next Annual Session of the American Medical Association are now being received. All Fellows of the American Medical Association are eligible. The program will be assembled in the early part of January 1946. Essayists who are not Fellows of the American Medical Association may be accepted by invitation.

All applications which were received for the 1945 meeting, which was not held because of the war, will be considered by the committee.

Applications should be addressed to Dr. Nelson Paul Anderson, Secretary of the Section on Dermatology and Syphilology, 2007 Wilshire Boulevard, Los Angeles 5, Calif.

Book Reviews

Approved Laboratory Technique. By John A. Kolmer, M.D., LL.D., and Fred Boerner, V.M.D. Fourth edition. Price, $10. Pp. 1,017, with 548 black and white illustrations. New York: D. Appleton-Century Company, Inc., 1945.

No matter how well trained and how well read a physician may be, there are times when he must find himself in a void when he studies laboratory reports, which are becoming more and more frequent and complicated as medical science advances. While dependency on laboratory procedure is particularly true of the physician of the hospitalized patient, it also is becoming increasingly necessary to the physician in resolving many of the problems in diagnosis which are so intriguing in the private office. Also, many physicians are unaware as to what is involved in the laboratory when they make requests for laboratory examinations. Every dermatologist should know at least what was behind the scenes in the laboratory; teachers, particularly, should be prepared to round out their presentations to students in this connection. In these circumstances, the busier the physician, the more welcome is a book—such as this one by Kolmer and Boerner—which will fill the void.

The authors grant that the book does not cover the changes due to disease and their interpretation; it is confined largely to methods and normal values. This will be disappointing to most dermatologists, particularly the absence of "interpretation." However, the science of laboratory examination has expanded to such an extent that the authors are perhaps justified in selecting the phase of the subject that they did, so that they could treat it comprehensibly and exhaustively. Interpretations, it is true, can be found elsewhere, but in the opinion of this reviewer it should be still practicable to include sufficient in this book to stimulate additional interest in the laboratory technician, who is working more or less blindly, to say nothing of what it means to the physician. For future editions this point should be seriously considered.

This comprehensive book of more than one thousand pages covers all kinds of examinations that might be demanded from a medical laboratory, ranging through such topics as the treatment of laboratory accidents and the preparation of glassware and culture mediums to the actual performance of tests. Most of the subject matter does not immediately concern the clinical dermatologist. Scattered through the book, though, are subjects of which he should have knowledge. Of high importance is the separate section which deals with methods for the collection and handling of material for bacteriologic examinations. The many tests of serum and spinal fluid for syphilis are exhaustively and authoritatively presented by such experts as Kolmer and Boerner. By way of illustrating special needs of dermatologists, the following subjects deserve mention: technic of sternal biopsy, tests for porphyrin and melanin in the urine, the Fishberg test for hepatic function (which is so important in the rapid treatment of syphilis), the congo red test, the fluorescent dye method for demonstrating Mycobacterium tuberculosis and Mycobacterium leprae, the detection of amebas, the oil method for demonstrating the presence of mites, tests for heterophile antibodies and technics for determining the blood chlosterol level of blood, the sulfanilamide content of urine, the concentration of vitamins in blood and urine and the bromide content in the blood and urine. The hematologic methods that are described concern the dermatologist in the difficult field of the leukoses and to a less degree in the erythroses (sickle cell anemia, hypochromic anemia and others). For the purposes of the dermatologist the section on mycology is decidedly inferior to that which is offered in the texts sponsored by dermatologists. No doubt, the inaccuracies and organization of this new section will be corrected in future editions. The section on animal parasites shares in the inaccuracies, particularly in the spelling of names of the parasitic species. Needless to say, the authors have aimed to bring all methods to date and to omit those that have been replaced by better ones; this is highly important, considering the rapidity with which methods are improved.

In short, the book in its entirety will interest only those dermatologists (mainly teachers) who are directing or conducting laboratory investigations. The parts that are of interest to the average dermatologist are scattered widely in the book but can be easily found by consulting the excellent index. Without question, the book can be recommended for use by present day trainees in dermatology and by the many dermatologists who want to "brush up" on the special topics which have been partially indicated in the preceding paragraph, whether for immediately practical reasons or only for purposes of general information in medicine at large.

Directory of Dermatologic Societies *

INTERNATIONAL

Tenth International Congress of Dermatology and Syphilology

Oliver S. Ormsby, President, 25 E. Washington St., Chicago.
Paul A. O'Leary, Secretary-General, 102–2d Ave. S. W., Rochester, Minn.
Place: New York. Time: Postponed indefinitely.

Pan American Medical Association, Section of Dermatology and Syphilology

J. J. Eller, President, 745–5th Ave., New York.
Austin W. Cheever, Secretary, 464 Beacon St., Boston.

FOREIGN

British Association of Dermatology and Syphilology (Canadian Branch)

D. E. H. Cleveland, President, 925 W. Georgia St., Vancouver, B. C.
Donald H. Williams, Secretary-Treasurer, 925 W. Georgia St., Vancouver, B. C.

Hawaii Dermatological Society

James T. Wayson, President, Territorial Office Bldg., Honolulu.
Harry L. Arnold Jr., Secretary, 881 Young St., Honolulu.

Royal Society of Medicine, Section of Dermatology

M. Sydney Thomson, President, King's College Hospital, Denmark Hill, London S. E. 5, England.
Geoffrey R. Edwards, Secretary, 1 Wimpole St., London W. 1, England.

Sociedad Mexicana de Dermatología

Mario Salazar Mallén, President, Ignacio Ramírez 11, México, D. F., Mexico.
Fernando Latapí, Permanent Secretary, Zacatecas 220-6, México, D. F., Mexico.

NATIONAL

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Clyde L. Cummer, Chairman, 1422 Euclid Ave., Cleveland.
Nelson P. Anderson, Secretary, 2007 Wilshire Blvd., Los Angeles.

American Academy of Dermatology and Syphilology

George M. MacKee, President, 999–5th Ave., New York.
Earl D. Osborne, Secretary, 471 Delaware Ave., Buffalo, N. Y.

American Board of Dermatology and Syphilology

Howard Fox, President, 140 E. 54th St., New York.
George M. Lewis, Secretary-Treasurer, 66 E. 66th St., New York.

American Dermatological Association

Fred D. Weidman, President, Medical Laboratories, University of Pennsylvania, Philadelphia.
Harry R. Foerster, Secretary, 208 E. Wisconsin Ave., Milwaukee.

Society for Investigative Dermatology

Henry E. Michelson, President, 715 Medical Arts Bldg., Minneapolis.
S. William Becker, Secretary, 55 E. Washington St., Chicago 2.

SECTIONAL

Central States Dermatological Association

Frank R. Menagh, President, Henry Ford Hospital, Detroit.
C. E. Reyner, Secretary-Treasurer, Henry Ford Hospital, Detroit.
Place: Harper Hospital, Detroit. Time: April 27, 1946.

Mississippi Valley Dermatological Society

Lawrence C. Goldberg, Secretary-Treasurer, 623 Doctors Bldg., Cincinnati.
Place: Chicago.

New England Dermatological Society

Bernard Appel, President, 281 Ocean Ave., Lynn, Mass.
G. Marshall Crawford, Secretary, 1101 Beacon St., Brookline, Mass.

Northern New Jersey Dermatological Society

John Kiley, President, 94 Park St., Montclair.
Henry Abel, Secretary, 339 Union Ave., Elizabeth.
Place: Academy of Medicine of Northern New Jersey, Newark. Time: Third Tuesday of March, April, October and December.

Southeastern Dermatological Association

Howard Hailey, Chairman, 107 Doctors Bldg., Atlanta, Ga.
A. H. Lancaster, Secretary, P. O. Box 585, Knoxville, Tenn.

Southern Medical Association, Section on Dermatology and Syphilology

Charles O. King, Chairman, Medical Arts Bldg., Birmingham 5, Ala.
Francis A. Ellis, Secretary, 8 E. Madison St., Baltimore 2.

Southwestern Dermatological Society

Louis Jekel, President, Professional Bldg., Phoenix, Ariz.
George K. Rogers, Secretary, Grunow Memorial, Phoenix, Ariz.

STATE

California Medical Association, Scientific Assembly, Dermatology and Syphilology Section

Irving R. Bancroft, Chairman, 1052 W. 6th St., Los Angeles.
Chris Halloran, Secretary, 1052 W. 6th St., Los Angeles.

Connecticut State Medical Society, Section on Dermatology

Harry Bailey, Chairman, 242 Trumbull St., Hartford.
Louis O'Brasky, Secretary, 1172 Chapel St., New Haven.

* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

FLORIDA SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

J. Frank Wilson, Chairman, 415 Greenleaf Bldg., Jacksonville, Fla.

Wesley W. Wilson, Secretary, 322 Citizen's Bldg., Tampa, Fla.

LOUISIANA DERMATOLOGICAL SOCIETY

M. T. Van Studdiford, President, 912 Pere Marquette Bldg., New Orleans.

R. A. Oriol, Secretary-Treasurer, 921 Canal St., New Orleans.

MASSACHUSETTS MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

John G. Downing, President, 520 Commonwealth Ave., Boston.

G. Marshall Crawford, Secretary, 1101 Beacon St., Boston.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, SECTION ON DERMATOLOGY AND SYPHILOLOGY

C. H. Peachey, Chairman, 197 S. Goodman St., Rochester, N. Y.

E. W. Abramowitz, Secretary, 853–7th Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON DERMATOLOGY

Bernhard A. Goldmann, Chairman, 500 Penn Ave., Pittsburgh.

M. A. Pettler, Secretary, 1319–8th Ave., Beaver Falls.

MICHIGAN STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Kenneth Moore, Chairman, 1613 Union Industrial Bank Bldg., Flint.

Ruth Herrick, Secretary, 26 Sheldon Ave. S.E., Grand Rapids 2.

MINNESOTA DERMATOLOGICAL SOCIETY

S. E. Sweitzer, President, 825 Nicollet Ave., Minneapolis.

Harry A. Cumming, Secretary-Treasurer, 419 Medical Arts Bldg., Minneapolis.

Time: First Friday in January, April, July and October.

OKLAHOMA STATE DERMATOLOGICAL SOCIETY

John H. Lamb Jr., President, Medical Arts Bldg., Oklahoma City.

M. M. Wickham, Secretary, 716 W. Symmes St., Norman.

TEXAS DERMATOLOGICAL SOCIETY

J. Lewis Pipkin, President, 705 E. Houston St., San Antonio.

Duncan O. Poth, Secretary-Treasurer, 414 Navarro St., San Antonio.

LOCAL

BALTIMORE-WASHINGTON DERMATOLOGICAL SOCIETY

Hayden Kirby-Smith, Chairman, 1610—20th St. N. W., Washington, D. C.

Lawrence B. McCaleb, Secretary-Treasurer, 1835 I St. N. W., Washington, D. C.

Place: Alternate cities. Time: Third Thursday of each month.

BRONX DERMATOLOGICAL SOCIETY

David Bloom, President, 135 E. 50th St., New York.

Henry Silver, Secretary, 290 West End Ave., New York.

Time: Fourth Thursday of each month from October to May, inclusive.

BROOKLYN DERMATOLOGICAL SOCIETY

Joel Schweig, President, 47 E. 61st St., New York.

Nathan Pensky, Secretary, 2167–81st St., Brooklyn.

Time: Third Monday of each month except June, July, August and September.

BUFFALO-ROCHESTER DERMATOLOGICAL SOCIETY

James W. Jordon, President, 471 Delaware Ave., Buffalo.

Frank A. Dolce, Secretary-Treasurer, 468 Delaware Ave., Buffalo.

CENTRAL NEW YORK DERMATOLOGICAL SOCIETY

Albert Van Vranken, President, 1565 Union St., Schenectady.

Maxwell C. Snider, Secretary, 106 Oak St., Binghampton.

CHICAGO DERMATOLOGICAL SOCIETY

Frederick R. Schmidt, President, 122 S. Michigan Blvd., Chicago 3.

Marcus R. Caro, Secretary-Treasurer, 25 E. Washington St., Chicago.

CINCINNATI SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

R. G. Senour, President, 937 Carew Tower, Cincinnati 2.

Alfred L. Weiner, Secretary-Treasurer, Union Central Bldg., Cincinnati 2.

Place: Cincinnati. Time: First Wednesday of each month, except July, August and September.

CLEVELAND DERMATOLOGICAL SOCIETY

L. L. Praver, President, 289 E. State St., Columbus, Ohio.

G. W. Binkley, Secretary, 10515 Carnegie Ave. S. E., Cleveland 6.

Time: Fourth Thursday of each month from September to May, inclusive.

DETROIT DERMATOLOGICAL SOCIETY

Harther L. Keim, President, 1110 Eaton Tower, Detroit 26.

C. E. Reyner, Secretary-Treasurer, Henry Ford Hospital, Detroit 2.

KANSAS CITY (MO.) DERMATOLOGICAL SOCIETY

C. C. Dennie, President, 1103 Grand Ave., Kansas City.

Thomas B. Hall, Secretary, 902 Professional Bldg., Kansas City.

LOS ANGELES DERMATOLOGICAL SOCIETY

Clement E. Counter, President, 117 E. 8th St., Long Beach, Calif.

Maximilian E. Obermayer, Secretary, 1930 Wilshire Blvd., Los Angeles.

Time: Second Tuesday of each month, October to May, inclusive.

MANHATTAN DERMATOLOGIC SOCIETY

George M. Lewis, Chairman, 66 E. 66th St., New York.

Wilbert Sachs, Secretary, 6 E. 85th St., New York.

Metropolitan Dermatological Society

James Lowry Miller, President, 371 Park Ave., New York 22.

Leslie P. Barker, Secretary, 120 E. 75th St., New York.

Montreal Dermatological Society

Paul Poirier, President, 456 Sherbrooke St. E., Montreal, Canada.

Alphonse Bernier, Secretary, 3995 St. Denis St., Montreal.

New York Academy of Medicine, Section of Dermatology and Syphilis

Harry C. Saunders, Chairman, 159 W. 87th St., New York.

Frank Vero, Secretary, 1070 Park Ave., New York.

New York Dermatological Society

H. J. Schwartz, President, 100 Central Park W., New York.

George C. Andrews, Secretary-Treasurer, 115 E. 61st St., New York.

Omaha Dermatological Society

Donald J. Wilson, President, 1113 Medical Arts Bldg., Omaha.

Leonard J. Owen, Secretary-Treasurer, 954 Stuart Bldg. Lincoln, Neb.

Philadelphia Dermatological Society

Donald M. Pillsbury, Chairman, 133 S. 36th St., Philadelphia.

Reuben Friedman, Secretary, 877 N. 6th St., Philadelphia 23.

Time: Third Friday of every month except June, July and August.

Pittsburgh Dermatological Society

Emerson Gillespie, President, First National Bank Bldg., Canton, Ohio.

Townsend W. Baer, Secretary, Jenkins Arcade Bldg., Pittsburgh 22.

Time: Third Thursday of every month except July and August.

St. Louis Dermatological Society

Clinton W. Lane, President, Metropolitan Bldg., St. Louis.

Joseph Grindon Jr., Secretary-Treasurer, 323 Lister Bldg., St. Louis.

Place: Barnard Free Skin and Cancer Hospital.

Time: 8 p. m., third Monday of each month.

San Francisco Dermatological Society

Otto L. E. Schmidt, President, Stanford University Hospital, San Francisco.

Frances M. Keddie, Secretary-Treasurer, University of California Hospital, San Francisco.

Time: Third Friday of February, April, September and November.

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*Beerman, Shaffer, and Livingood, *J. Amer. Med. Assn.* (1942), 120:333.

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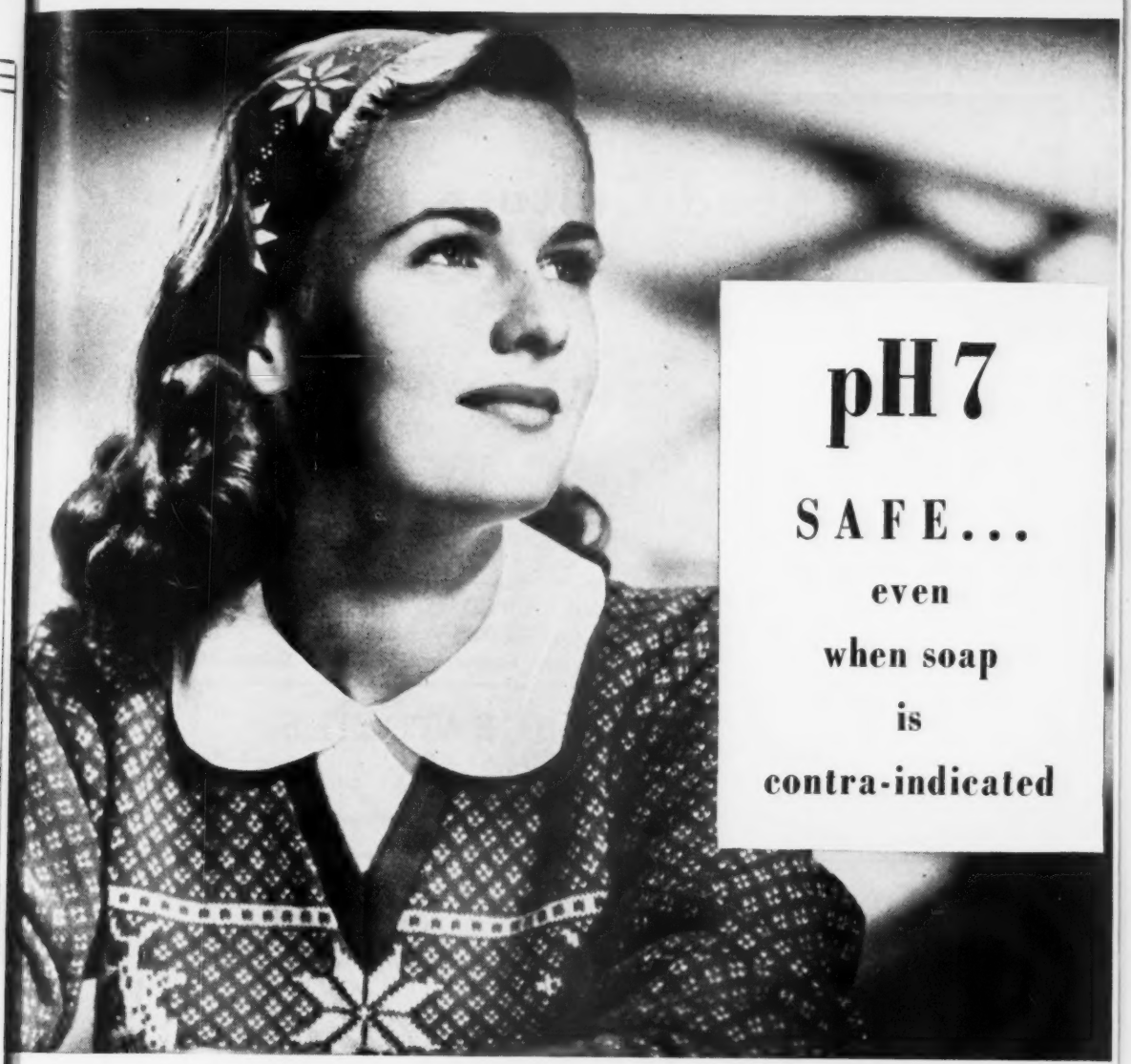

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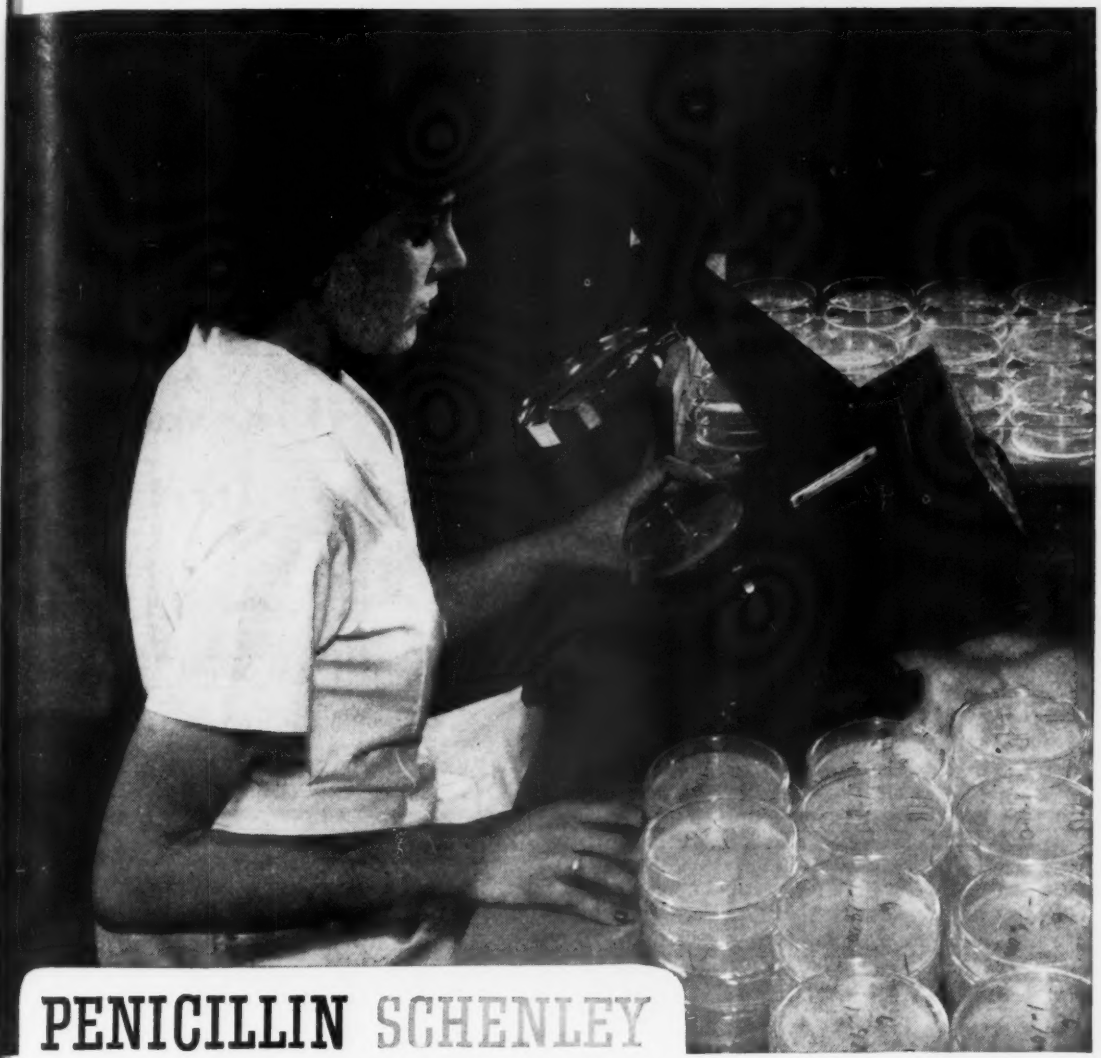

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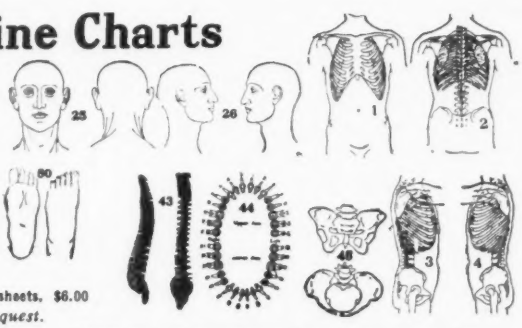

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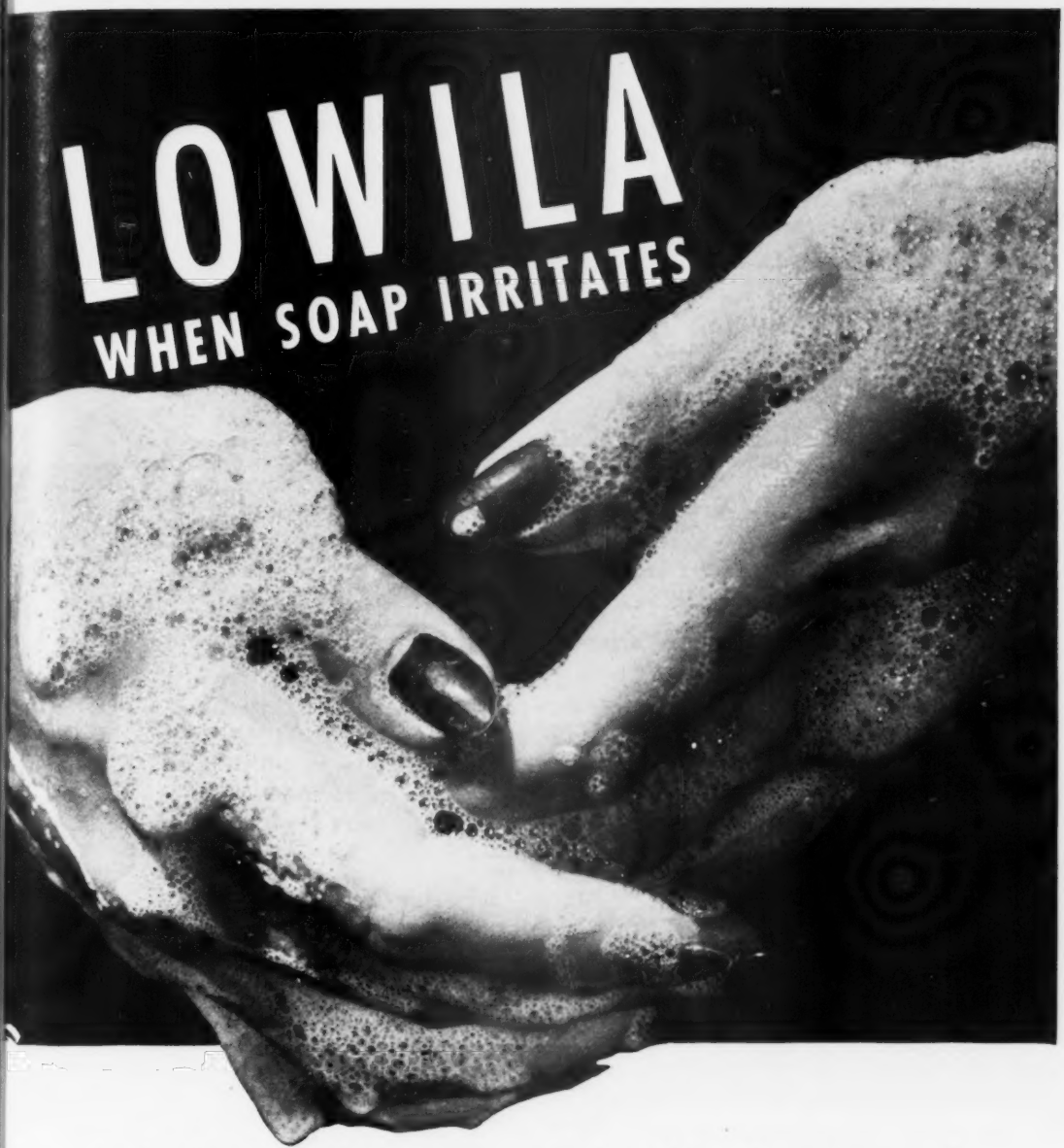

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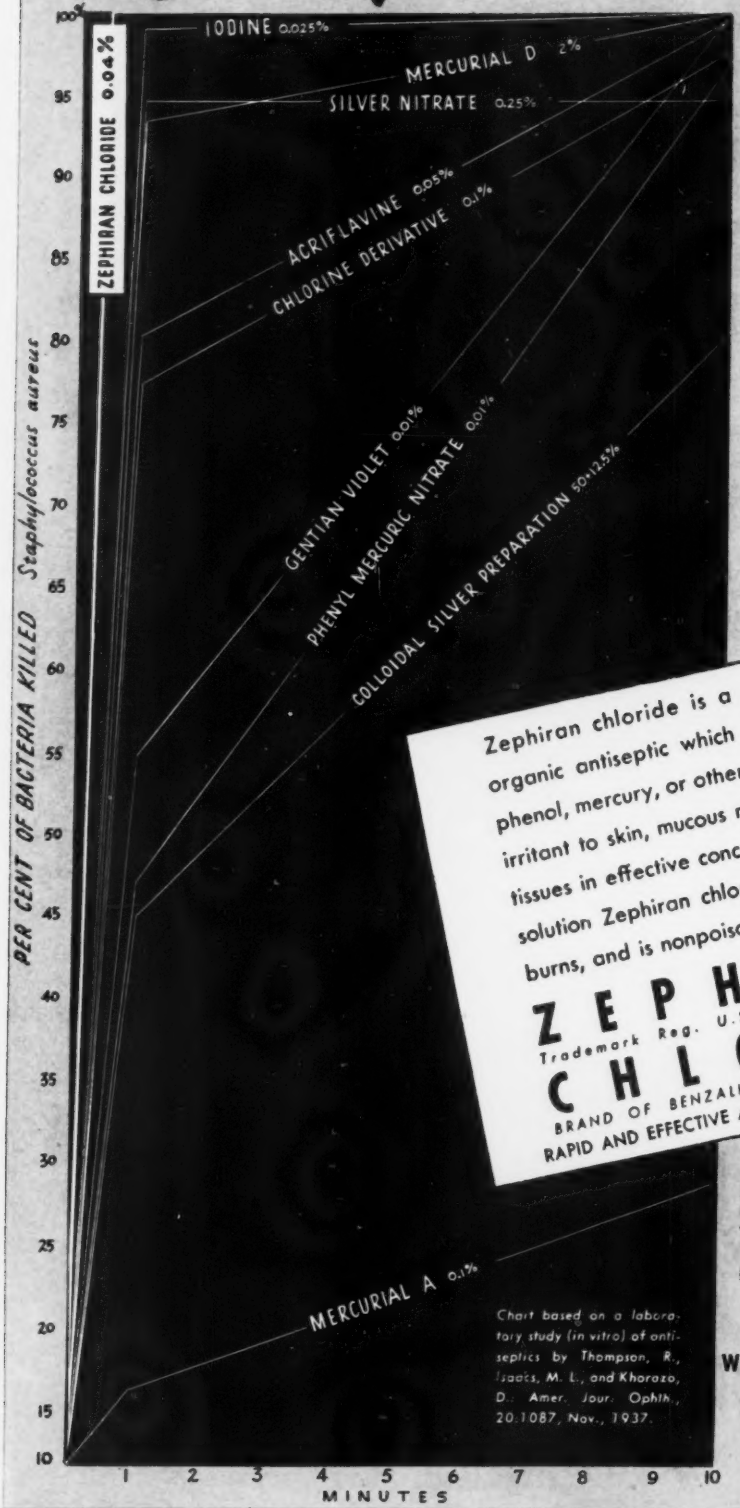

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